PRINCESS MARGARET CANCER CENTRE
CLINICAL PRACTICE GUIDELINES

HEAD AND NECK

LARYNX
# 1. INTRODUCTION

# 2. PREVENTION

# 3. SCREENING AND EARLY DETECTION

# 4. DIAGNOSIS

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1. **Introduction**
   - Laryngeal cancer represents 2% of all cancers and is the most common head and neck cancer excluding skin cancer.
   - Carcinomas of the larynx are closely related to cigarette smoking, and evidence supporting a link with heavy marijuana smoking is mounting.
   - Heavy alcohol intake is probably more important for supraglottic as well as hypopharyngeal sites, as compared to glottis and subglottis.
     - Combined alcohol and tobacco use results in elevated risk in a multiplicative (rather than additive) fashion.
   - The role of Human Papilloma Virus (HPV) in genesis of laryngeal cancer is unclear.

2. **Prevention**
   - The role of smoking cessation is important in the prevention of head and neck squamous cells cancer. Some studies suggest that in ex-smokers after 5 years of abstinence the risk of tobacco related cancers of upper aerodigestive tract declines.

3. **Screening and Early Detection**
   - There is currently no role for screening in laryngeal cancer.

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.
         - For current smokers smoking cessation is to be advised and a referral to cessation services made.
       - alcohol history in standard drinks/week;
         - None / Light <10 drink/wk /
         - Mod 10-20 /
         - Heavy >20.
     - Record stage (current edition TNM).
   - Specify location of primary including dimensions and involvement of anatomic subsites:
     - glottic.
• subglottic
• supraglottic

- 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
  - UHN pathology review; molecular diagnostic testing (e.g. HPV status), if indicated
- CT scan Head and Neck
- PET/CT scan for N+ for RT planning
- CT thorax
- 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
- Almost all tumors arise from epithelium lining the larynx and are squamous cell carcinoma or one of the variants
  - The differentiation between carcinoma in situ, dysplasia, squamous cell carcinoma with microinvasion or true invasion may be difficult in some cases and relies heavily on sufficient biopsy and expert pathologist interpretation.
  - Verrucous carcinomas do occur in 1-2% of vocal cord cancers. They exhibit less aggressive behavior and are less responsive to radiation than surgery
  - Basaloid squamous carcinoma consider HPV testing.
  - It is very rare for a sarcoma to present with a carcinoma and most are actually “spindle cell carcinoma” i.e. squamous cell carcinoma.
- Other histological types occur infrequently:
  - Atypical carcinoids, lymphomas, lymphoma and plasmacytoma are very rare
  - Small cell neuroendocrine tumours are rare in supraglottis but should be identified given their potential for rapid growth, early dissemination and responsiveness to chemotherapy.
- Pathology reporting (for surgical specimens) should follow a standard format for larynx carcinoma, and include the following SYNOPTIC DATA, as per College of American Pathologists 2011 cancer protocols, (see [www.cap.org](http://www.cap.org) for full detail):
  - Specimen:
  - Procedure:
  - Unopened Specimen Size:
    - Greatest dimension:
• Additional dimension(s):
  o Tumor Laterality:
  o Site:
    ▪ Additional Sites Involved by Tumor:
    ▪ Tumor Focality:
  o Histologic Type:
    ▪ Histologic Grade:
  o Tumor Size:
    ▪ Additional dimension(s):
  o Margins:
    ▪ Distance of tumor from closest margin:
    ▪ Margin(s):
    ▪ Margin status for carcinoma in situ:
  o Lymph-Vascular Invasion:
  o Perineural Invasion:
  o 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:
  o TNM Descriptors:
    ▪ Primary Tumor (pT):
    ▪ Nodes (pN):
    ▪ Distant Metastasis (pM):

6. Management

Overall Management Approach
• These guidelines apply to patients with SCC of the larynx
• General management approach is a radical radiotherapy approach +/- chemotherapy and neck dissection for disease in the neck as required reserving total laryngectomy, hemilaryngectomy for radiation failures
• Transoral laser resection/ “cold steel” resection of Tis or T1a
• Surgical resection with post-operative radiotherapy or chemoradiotherapy is reserved for gross extralaryngeal extension (T4a) or when the likelihood of a functional larynx or pharynx after primary radiotherapy or chemoradiotherapy is minimal (see below)
• All patients should be assessed for inclusion on available current trial protocols and, if eligible and appropriate, offered inclusion on trial

Tis, T1a, N0 Glottic
Treatment Options:

- Radical radiotherapy
  - 51 Gy in 20 fractions, over 4 weeks (5 fractions/week)
  - 66 Gy in 33 fractions DAHANCA schedule (6 fractions/week), an option for bulky T1a lesions (e.g. exophytic, full length of cord involved)

- Surgical Resection [see surgical guideline, below]

T1b N0 Glottic

- Radical radiotherapy
  - 66 Gy in 33 fractions DAHANCA schedule (6 fractions/week)

T2 N0 Glottic

- Radical Radiotherapy
  - 66 Gy in 33 fractions, DAHANCA schedule (6 fractions/wk) for superficial disease with normal cord mobility
  - 70 Gy in 35 fractions, over 6 weeks DAHANCA schedule (6 fractions/wk) for bulky disease, especially with impaired cord mobility

T1/2 N0 Supra-glottis

- Radical Radiotherapy
  - 70 Gy in 35 fractions, over 6 weeks DAHANCA schedule (6 fractions/wk)
- Surgical resection [see surgical guideline, below]

T1/T2 N1, T3N0

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

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)

T3 N1, T1-T3 N2-N3

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)
**T4a N0-N3**

*Primary surgical resection and post-operative radiation preferred in patients with bulky extralaryngeal extension.*

**Patients unfit for surgery or declining surgery**

- **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

- **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

**T4b N0-N3**

- **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

- **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
Standard Post-Operative Radiotherapy - Adjuvant (any larynx site)

- Consider adjuvant radiotherapy for the following:
  - Primary site:
    - T3-T4
    - Microscopic margins <5mm (discuss with surgeon any intra-operative revision)
    - >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 >2mm)

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
    - Glottis
      - T1a – b: transoral laser resection or narrow field radiotherapy
        - N0: no neck treatment
        - N+: definitive treatment of neck (surgery or radiotherapy)
      - T2: hemilaryngectomy or suprocrioid laryngectomy with wide margin
- N0: elective neck treatment
- T2 – T3: radiotherapy vs chemoradiotherapy
  - N0: elective neck treatment
  - N+: definitive treatment of neck
- 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

  **Supraglottis**
  - T1: transoral laser resection (if minimal post-operative morbidity is anticipated) or organ preservation strategies
    - N0: elective neck treatment
    - N+: definitive neck treatment
  - T2: hemilaryngectomy or supracricoid laryngectomy with wide margin
    - N0: elective neck treatment
  - T2 – 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

  **Subglottis**
  - T1 – T3: organ preservation strategies
    - N0: elective neck treatment
    - N+: definitive neck treatment
• T4a: total laryngectomy and bilateral neck dissections (levels II – IV, VI)
  o +/- primary tracheoesophageal puncture
  o Fasciocutaneous microvascular free tissue transfer vs pectoralis major myocutaneous flap if insufficient mucosa for closure of neopharynx
  o Adjuvant radiotherapy or chemoradiotherapy where appropriate
  o In selected low volume T4a disease and residual laryngeal function, consideration of laryngeal preservation protocol
• T4b: tracheostomy for airway control, otherwise inoperable
  o Consider organ preservation strategy in select patients

• Salvage treatment (recurrence or persistence following treatment)
  o Primary site
    ▪ Salvage of transoral laser resection
      • Repeat transoral laser resection, or radiotherapy
    ▪ Localized and limited glottic or supraglottic disease following organ preservation protocols
      • Consider partial laryngectomy (open or transoral)
        o Must include initial tumor extent in salvage resection
        o If open hemilaryngectomy, utilize temporoparietal fascial microvascular free tissue transfer to provide vascularized tissue to region
    ▪ All subsites and stages of recurrence (except T4b)
      • Salvage total laryngectomy and bilateral neck dissections (levels II – IV, VI)
        o Fasciocutaneous microvascular free tissue transfer vs pectoralis major myocutaneous flap if insufficient mucosa for closure of neopharynx or poor quality of native tissue
        o In chemoradiation failure, strongly consider vascularized soft tissue reconstruction for augmentation in the majority of patients
  o 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

*Standard Treatment*
- **CONCURRENT CHEMO-RADIOThERAPY:**
  - **DEFINITIVE:**
    - Cisplatin 100mg/m², concurrent with weeks 1, 4, 7 of radiotherapy
  - **POST-OPERATIVE:**
    - Cisplatin 100mg/m², concurrent with weeks 1, 4 of radiotherapy

- **CONCURRENT CHEMO-RADIOThERAPY:**
  - **DEFINITIVE:**
    - Cisplatin 100mg/m², concurrent with weeks 1, 4, 7 of radiotherapy
  - **POST-OPERATIVE:**
    - Cisplatin 100mg/m², concurrent with weeks 1, 4 of radiotherapy

- **SETTING:**
  - Overnight admission in inpatient chemotherapy suite

- **Pre-treatment Assessment:**
  - Bloodwork: CBC, lytes, creatinine, liver function, hepatitis B and C profile, weight, height and BSA.

- **Pre-Medication / Hydration**
  - Anti-emetics:
    - ondansetron 16 mg IV q24hrs day 1,2 over 15 minutes
    - dexamethasone 10 mg IV day 1 (dose reduction or omission based on Hep B profile may occur), 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
    - dexamethasone 2 mg IV-int over 15 minutes q12hrs for 3 doses while in hospital, starting with the second dose of ondansetron (dose reduction of omission depending on Hep B profile may occur)

- **CHEMO: CISPLATIN 100mg/m² 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
o dose reduction / delay of chemotherapy dose should be considered for toxicities including (but not limited to):

- **Cytopenia**
  - Absolute neutrophil count (ANC)
    - 1-1.4 x 10^9/L: consider delay for 1 week, or 75% dose reduction
    - <1.0 x 10^9/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
  - Appropriate management of constipation with stool softeners and laxatives if required

### 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, hepatitis B and C profile, weight, height and BSA.
  - **Pre-Medication / Hydration**
    - Anti-emetics:
      - dexamethasone 8mg PO or IV at least 1 hour prior to chemotherapy
      - ondansetron 16 mg po or IV starting at least 1 hour prior to chemotherapy
    - Others:
  
  Last Revision Date – July 2019
- Magnesium sulfate 2g IV in normal saline 250 ml over 1 hour only if magnesium level = 0.5-0.6 mmol/L (call physician for magnesium level less than 0.5 mmol/L.

  o CHEMO:
    - CISPLATIN 40 mg/m² IV in 500 cc normal saline, over 1 hrs
  o Post-chemo supportive care:
    - Hydration 500 cc normal saline over 30-60 minutes
    - Ondansetron 16 mg PO day 2
    - Dexamethasone 4mg BID PO days 2-3
    - Prochlorperazine 10mg Q6H PRN

  o dose reduction / delay of chemotherapy dose should be considered for toxicities including (but not limited to):
    - Cytopenia
      - Absolute neutrophil count (ANC)
        - 1-1.4 x 10⁹/L: consider delay for 1 week, or 75% dose reduction
        - <1.0 x 10⁹/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
  o 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
    - Appropriate management of constipation with stool softeners and laxatives if required

### 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
- Assessment of airway patency and prophylactic tracheostomy prior to CT Simulation if required
- Current smokers counselled to stop smoking and referred to cessation services
- Audiology
  - Pts receiving platinum-type chemotherapy
  - Pts receiving high-dose adjacent to auditory apparatus
- Medical Oncology assessment (in patients potentially eligible for chemotherapy)
- 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

**PLANNING**

**DEFINITION / DELINEATION of TARGETS:**

- PRIMARY
  - **T1a/Tis NO glottic primary**
    - GTV: gross disease
    - CTV:
      - High-dose (5100cGy/20 fr): GTV + 0.3cm (may increase to 0.5cm where there is uncertainty regarding GTV extent)
      - Low-dose (4500cGy/20 fr): whole vocal cord + 1.0cm
    - PTV = 0.5cm radially with 1.0cm superior and inferior expansion (a greater PTV expansion may be required if a larger target volume motion is expected or seen)
  - **T1b/T2 NO glottic primary**
    - GTV: gross disease
    - CTV:
      - High-dose: GTV + 0.3cm (may increase to 0.5cm where there is uncertainty regarding GTV extent)
      - Low-dose: GTV+ cord involved side + 1.0cm
    - PTV = 0.5cm radially with 1.0cm superior and inferior expansion (a greater PTV expansion may be required if a larger target volume motion is expected or seen)
  - **OTHER PRIMARY SUBSITES:** Glottic T1/T2, N2/3; T3/T4, any N; Supraglottis & Subglottis T1/T2 N+; T3/T4 any N
    - GTV: Gross disease
• CTV:
  o High-dose GTV + 0.3cm (may increase to 0.5cm where there is uncertainty regarding GTV extent)
  o Low-dose GTV + cord involved side + 1.0cm
• PTV = 0.5cm radially with 1.0cm superior and inferior expansion (a greater PTV expansion may be required if a larger target volume motion is expected or seen)
  ▪ USE of BOLUS (0.5cm) should be considered for lesions involving anterior commissure, or where CTV extends close to skin surface, to ensure adequate dose coverage of the target volumes

  o NECK:
    ▪ GTV(s)
    ▪ CTV
      • High-dose: GTV (nodes) + 0.5cm
        o Standard dose / fractionation 70Gy
        o HARDWINS 64Gy
      • Intermediate-dose (indeterminate lymph nodes < 1cm)
        o Standard dose / fractionation 63Gy
        o HARDWINS 56Gy
      • Low-dose (elective neck, levels 2-4)
        o Standard dose / fractionation 56Gy
        o HARDWINS 46Gy
        o (or no neck coverage in selected N0 cases)
    ▪ PTV = CTV + 0.5cm

TREATMENT

• CLINICAL CARE DURING RADIOTHERAPY:
  o Pts shall be reviewed by the RO at least weekly during RT
  o 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
  o Management of acute toxicities: refer to Nursing / Supportive Care guideline

6.4 Oncology Nursing Practice
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:
  o 2-6 weeks post radiotherapy
  o Q3 months or more frequent for two years
  o Q4 months or more frequent for third year
  o Q6 months or more frequent for years 4-5
- Investigations and assessment (follow-up):
  o Fibre-optic nasendoscopy
  o Imaging
    o CT head and neck at 10-12 weeks post-treatment
    o Other imaging as clinically indicated
- Pharyngeal function (speech/swallow), if indicated
- Dental assessment where applicable
- Audiometry 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