



**PRINCESS MARGARET CANCER CENTRE
CLINICAL PRACTICE GUIDELINES**

HEAD AND NECK

CARCINOMA UNKNOWN PRIMARY

Head & Neck Site Group – Carcinoma Unknown Primary

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1. Introduction

- Squamous cell carcinoma (SCC) of unknown primary site is relatively rare in the head and neck region. This is a diagnosis of exclusion, made in 1-7% of patients with head and neck cancer after evaluation for possible primary site
- The diagnosis of SCC is typically made from biopsy of involved lymph node(s) in the cervical region
- These guidelines refer to patients with SCC, poorly- or undifferentiated carcinoma of the head and neck region

2. Etiology & Prevention

- Etiology and risk factors should be considered as for the relevant carcinomas with an identifiable primary site, of the head and neck region i.e.
 - SCC of mucosal origin is known to be associated with tobacco use, and heavy alcohol intake
 - Oropharyngeal SCC is associated with human papilloma virus (HPV) infection in 50-70% of cases
 - Nasopharyngeal carcinoma (NPC) associated with Epstein-Barr virus (EBV) infection, and dietary factors (intake of dietary nitrosamines) and is endemic in populations from certain parts of the world (eg. southern China, northern Africa and the Mediterranean)
- Reduction in exposure to such causative agents as tobacco and alcohol could therefore reduce the incidence of these malignancies
- Refer to Clinical Guidelines for specific primary sites for further detail

3. Screening and Early Detection

- There is currently no role for screening for carcinoma of unknown primary of the Head and Neck region

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
 - Record smoking (in pack years), and alcohol history (standard drinks/week: None/Light <10 drink/wk/ Mod 10-20 / Heavy >20)
 - Record history of exposures to betel-nut, oral tobacco, or other carcinogens
 - Record geographic origin of patient or ancestors
 - Record stage (current edition TNM)
- Documentation of specific nodal level(s) involved

- Size and extent of nodal involvement (e.g. fixed/mobile)

Investigations (Baseline):

- Panendoscopy / examination under anaesthesia, and biopsies
 - Panendoscopy and biopsies
 - Ipsilateral presentation– ipsilateral biopsies:
 - nasopharynx, base of tongue, pyriform fossa and tonsillar fossa
 - bilateral tonsillectomy
 - Bilateral presentation – bilateral biopsies:
 - candidate primary sites
 - Bilateral tonsillectomy
- Biopsy (lymph node)
 - UHN pathology review
 - FNA with cell block (sufficient sample for immunohistochemistry); or core biopsy
 - For FNAB samples cytologist should be present for an on-site assessment during the collection and handling of the FNA sample to ensure adequacy
 - Molecular diagnostic testing including:
 - HPV status (p16 status); core biopsy preferred
 - EBV status (IHC or in-situ hybridisation) in high-risk population - see below
- CT scan Head and Neck
- MRI Head & Neck
- CT thorax; consider CT abdo/pelvis if left lvl IV LN
- PET scan
- Bloodwork: CBC, creatinine, electrolytes, liver function, glucose, coagulation studies (APTT, INR)
- Pregnancy test where indicated
- Other staging investigations as clinically indicated (bone scan, liver imaging, etc)
- Clinical photograph as indicated

5. Pathology

- Biopsies may demonstrate
 - Squamous cell carcinoma
 - Poorly differentiated carcinoma
 - Undifferentiated carcinoma
- Immunohistochemistry (IHC) is performed to exclude other histology in the case of poorly- or un-differentiated carcinomas
- Molecular diagnostic testing may be of assistance in identifying potential occult primary sites and should be undertaken including
 - HPV status (p16 status)

- EBV status: Epstein-Barr virus encoded RNA (EBER) as clinically indicated
- The guidelines for pathology reporting and information are applicable as for other head and neck subsites with an identifiable primary lesion (see relevant Clinical Practice Guidelines)

6. Management

Overall Management Approach

- These guidelines apply to patients with squamous cell carcinoma of unknown primary site of the head and neck region
- *Define High Risk Group for Nasopharyngeal Carcinoma*
 - lymphoepithelioma/undifferentiated carcinoma
 - Younger cohort (<40 years)
 - Non-smoker
 - Asian, Inuit, Polynesian ancestry, Mediterranean littoral, including North Africa
 - Isolated or dominant level 5 disease ; retropharyngeal (RPN) lymph node disease
 - EBV+
- *Define High Risk Group for Skin Carcinoma*
 - Squamous cell histology
 - Non-smoker / no history excess alcohol consumption
 - Fair complexion (e.g. Northern European ancestry)
 - Sun exposure with actinic changes / prior history skin SCC
 - immunocompromised
 - Periparotid / parotid involvement
- *Define High Risk Group for HPV+ Oropharyngeal Carcinoma*
 - Squamous cell histology, especially basaloid subtype
 - Non-smoker / no history excess alcohol consumption
 - History marijuana use
 - Cystic nodal disease
- All patients should be assessed for inclusion on available current trial protocols and, if eligible and appropriate, offered inclusion on trial

TREATMENT

T0, N1 level II or III squamous cell carcinoma

Standard Treatment - Primary Radiotherapy

- Radiotherapy volume:
 - Treat ipsilateral technique i.e. lymph nodes and candidate primary site(s) unless:
 - patient refusal
 - high risk group for carcinoma nasopharynx, and HPV+ group
 - Ipsilateral neck alone radiotherapy may be considered at discretion of treating physician, especially relevant to high risk skin cancer cases
- Radiotherapy dose:
 - Standard radiotherapy: 70Gy / 35 fractions (5 fractions/wk)
OR
 - 70Gy / 35 fractions (6 fractions/wk) DAHANCA
OR
 - 60 Gy in 25 fractions to the gross node, 50Gy in 25 fractions to subclinical disease sites (including candidate primary sites)
OR
 - 55Gy in 25 fractions for excised lymph node without extra-capsular extension (ECE), 50Gy in 25 fractions to subclinical disease sites (including candidate primary sites)

Standard Treatment - Primary Surgery

- Patients may be observed after a neck dissection:
 - Exceptions, patients with:
 - Risk factors for nasopharyngeal carcinoma
 - HPV+ patients
 - Indications for postoperative radiotherapy
- Postoperative radiotherapy to neck as for conventional indications i.e.
 - ECE, positive margins of resection

T0N1 level IV

- Treatment should be individualized based on risk factors, and patient characteristics

T0N1 level V

- Treatment should be individualized based on risk factors
- Strongly consider treating with bilateral technique to include nasopharynx
- Volumes:
 - GTV: gross nodes
 - CTV: 0.5 cm margin:
 - gross node
 - bilateral neck levels II-V

- nasopharynx
- tonsillar fossa and lateral pharyngeal wall
- base of tongue
- pyriform fossa

T0N1 Level I

- Treat ipsilateral technique with mouth open technique (mouth block/bite)
- Volumes:
 - GTV: gross nodes
 - CTV: 0.5 cm margin:
 - gross node
 - ipsilateral level I-II
 - ipsilateral oral cavity

T0N2A, B

- Treat bilateral technique, ipsilateral technique may be considered in selected cases (based on risk categories e.g. likely skin primary)
- Treat nasopharynx as indicated
- RADIOTHERAPY DOSE:
 - 70Gy / 35 fractions (5 fractions/wk) with concurrent chemotherapy (standard)
 - OR
 - HARDWINS (64Gy / 40 fractions bid)
 - DAHANCA (70Gy / 35 fractions (6 fractions/wk)

T0N2C

- Treat bilateral technique
- Treat nasopharynx as indicated
- Concurrent chemotherapy

T0N3

Resectable

- Primary surgery (neck dissection) preferred, unless
 - High risk for NPC
 - p16/HPV+
- post-operative radiotherapy
 - Treat bilateral technique
 - Consider concurrent chemotherapy for standard indications in post-operative setting (ECE, positive margin)
- Treat nasopharynx as indicated

Unresectable

- Treat bilateral technique
- Treat nasopharynx as indicated
- Concurrent chemo-radiation

Patients not suitable for radical treatment

Refer to separate guideline: Palliative Management of Patients with H&N malignancy

6.1 Surgery

- Initial treatment (no prior treatment administered)
 - Primary site
 - Perform pan-endoscopy and biopsy
 - Surgeon must be experienced in endoscopy
 - Must assess nasopharynx, oral cavity, oropharynx, larynx, hypopharynx, cervical/mid esophagus, and subglottis/trachea
 - Perform bilateral palatine tonsillectomies; biopsy suspicious lesions and bilateral base of tongue
 - Neck
 - N1: selective neck dissection or radiotherapy
 - N2 or greater: radiotherapy
- Salvage treatment (recurrence or persistence following treatment)
 - 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 outlined above (*Overall Management, 5*)
- For post-operative treatment for the indications listed above (positive margin, or extracapsular nodal extension)
- CONCURRENT CHEMO-RADIOTHERAPY:
 - DEFINITIVE:
 - Cisplatin $100\text{mg}/\text{m}^2$, concurrent with weeks 1, 4, 7 of radiotherapy
 - POST-OPERATIVE:
 - Cisplatin $100\text{mg}/\text{m}^2$, 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/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
- 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 or 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/m² loading dose week prior to radiotherapy, then 250mg/m² 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/m² 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 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
- Other precautions:
 - Potential mutagen: Women of childbearing age must practice an appropriate form of contraception while being treated.
 - Neutropenia: fever or 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 chemoRx
 - 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

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) where 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