PRINCESS MARGARET CANCER CENTRE
CLINICAL PRACTICE GUIDELINES

HEAD AND NECK

ORAL CAVITY SQUAMOUS CELL CARCINOMA
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1. **Introduction**
   - There are an estimated 266,000 new cases of oral cavity squamous cell carcinoma (SCC) worldwide each year.
   - SCC is the predominant tumor type (>90%) that occurs in the oral cavity, and will be discussed in this policy.
   - Other tumors of glandular, odontogenic, lymphoid or connective tissue origin may occur, but require separate consideration / treatment approach and are not included here.

2. **Prevention**
   - Factors associated with increased risk of oral cavity cancer include:
     - Tobacco use
     - Alcohol consumption: dose-related; and synergistic effect with tobacco
     - Betel-nut chewing
   - Exposure to ultraviolet light / sun exposure, and contact with smoking apparatus are associated with increased risk of lip cancers.
   - Programs directed at reduction / elimination of these substances are important in reducing the risk of oral cavity cancers.
   - Human papilloma virus (HPV) infection is associated with increased risk of oropharyngeal SCC, but HPV-associated SCC only associated with a very small fraction of oral cavity SCC.

3. **Screening and Early Detection**
   - There is at present no evidence for routine screening in oral cavity SCC, as there is no evidence that this improves mortality.

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 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 history of exposures to betel-nut, oral tobacco, or other carcinogens.
• Record stage (current edition TNM)
• Specify location of primary including dimensions and involvement of anatomic subsites:
  o buccal mucosa
  o oral tongue
  o floor of mouth
  o lip
  o retromolar trigone
  o hard palate mucosa
  o alveolus – upper and lower
• presence of premalignant changes (leukoplakic /erythroplakic lesions)
• Documentation of specific nodal level(s) involved
  o 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
• MRI Head and Neck if indicated
• 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)
• Clinical photograph as indicated

5. Pathology
• SCC are classified as well (Grade 1), moderately (Grade 2), or poorly-differentiated (Grade 3), although these are not perfectly correlated with prognosis
• Additional histological features including tumor size, tumor thickness, depth of invasion (DOI), lymphvascular space invasion (LVSI), perineural invasion (PNI), lymph node involvement (and extracapsular extension)
• SCC variants may occur in the oral cavity: verrucous, basaloïd, spindle cell, adenosquamous and others
• Precursor lesions (hyperplasia/dysplasia), clinically seen as leukoplakia/erythroplakia: the majority will not undergo malignant change. Dysplasia may be mild/moderate/severe.
• Pathology reporting (for surgical specimens) should follow a standard format for oral cavity carcinoma, and include the following SYNOPTIC DATA (according to College of American Pathologists 2017 cancer protocols, see www.cap.org for full detail):
  o Specimen:
  o Procedure:
  o Specimen Integrity:
6. Management

**Overall Management Approach**

- These guidelines apply to patients with squamous cell carcinoma of the oral cavity (buccal mucosa, oral tongue, floor of mouth, lip retromolar trigone, hard palate mucosa, alveolus – upper and lower)
- Organ and function preservation using surgery ± reconstruction and post-operative radiotherapy ± chemotherapy, or radical radiotherapy ± chemotherapy with salvage surgery as required
- All patients should be assessed for inclusion in available clinical trial protocols
• Post-operative radiotherapy should be ideally started within 6 weeks of surgery
• Brachytherapy is not routinely employed

Clinical TanyNanyM0, if resectable:
The standard approach is surgery +/- neck dissection

Except:
Primary radiotherapy +/- concurrent chemotherapy, considered when:
• Retromolar trigone primary, where either primary surgical, or primary radiotherapy may be appropriate depending on tumor and patient factors
  o (See guidelines for oropharynx primary for primary radiotherapy)
• surgical morbidity at primary site anticipated and considered not appropriate
• patient declines surgery
• unresectable neck disease, and primary not yet treated surgically
• unresectable neck and primary already resected:
  o assess risk to the primary and consider inclusion in radiotherapy volume

After surgery, patient to be seen back within 4 weeks for adjuvant treatment assessment:
• Review pathology
• Consider adjuvant radiotherapy for the following indications:
  o Primary site:
    ▪ T3-T4
    ▪ Microscopic margins <5mm are considered high risk for local recurrence.
      • The greatest risk is in patients with deep margins<5mm. Decisions with regard to recommending additional therapy should be made after discussion with the surgical team and consideration of the final margin (or revised margin)
    ▪ >1 additional features at primary:
      • High-grade disease (poorly-differentiated carcinoma)
      • Peri- neural invasion (PNI)
      • Lymph-vascular invasion (LVSI)
  o Neck
    ▪ Lymph node involvement at pathology:
      • ≥2 lymph nodes
      • Any lymph node >3 cm (N2+)
      • Level IV-V LN positive
      • Extracapsular extension (ECE)
    ▪ Patient cases with neck specimens containing < 18 lymph nodes should be reviewed with the surgical team and surgical pathology with regard to the comprehensiveness of the neck dissection. Patients with less than adequate dissections should be considered for adjuvant therapy based on the risk of neck disease associated with the primary site of disease (risk factors including):
      • Tumor thickness (>5mm)
• LVSI
• PNI
• Tumor size
• Site
  o Floor of mouth
  o Oral tongue
• Consider adjuvant chemo-radiotherapy if:
  o ECE
  o Positive margins either at the primary site, or within the neck specimen

STANDARD POST-OPERATIVE RADIOTHERAPY DOSE (any oral cavity site)

• High risk post-op radiotherapy with residual/recurrent gross disease
  o 70 Gy in 35 fractions (high volume disease)
  o 69.96Gy in 33 fractions (low volume disease)
  o 66Gy in 30 fractions (low volume disease)
• High risk post-op radiotherapy (no gross residual disease)
  o High risk CTV (positive margins, ECE): 66Gy in 33 fractions over 6.5 weeks (5 fractions/wk)
  o Surgical bed/HTV: 60Gy in 33 fractions over 6.5 weeks (5 fractions/wk)
  o Low risk/Elective nodal regions: 56Gy in 33 fractions over 6.5 weeks (5 fractions/wk)
• Standard risk post-op radiotherapy:
  o 60Gy in 30 fractions over 6 weeks (5 fractions/wk) to HTV
  o 54Gy in 30 fractions over 6 weeks (5 fractions/wk) to low risk CTV

Patients not suitable for radical treatment
Refer to separate guideline: Palliative Management of Patients with H&N malignancy (SECTION 12)

6.1 Surgery

• Primary site
  o T1 – T4a: surgical resection
    ▪ In selected patients with advanced tumors where surgical resection would significantly compromise oral function, consider organ preservation strategies
  o T4b: tracheostomy if needed for airway control, otherwise inoperable
    ▪ Consider organ preservation strategy in select patients (with appropriate performance status)
  o Mandibulectomy considerations
    ▪ If no periosteal involvement: resect periosteum as margin
    ▪ If periosteum or minimal cortical bone involvement: perform marginal mandibulectomy
If marrow space involvement: perform segmental mandibulectomy

Subsite specific reconstructive considerations

Oral tongue or floor of mouth
- If expect minimal tethering of tongue: consider primary closure, split thickness skin graft, or healing by secondary intent
- Otherwise consider microvascular free tissue transfer

Lip
- If < 1/2 of lip involved: primary closure
- If > 1/2 to full lip involved: local rotation flaps
- If full lip or greater involved: consider microvascular free tissue transfer

Buccal
- If T2 or greater with involvement of the buccinators muscle, consider microvascular free tissue transfer to avoid disabling trismus

Retromolar trigone
- Often requires resection of mandible (see mandible reconstruction below)

Alveolus
- Local mucosal advancement flaps vs microvascular free tissue transfer

Mandible reconstruction
- If marginal mandibulectomy, dentulous, and ~1/2 vertical height remains: no reconstruction
- If marginal mandibulectomy and edentulous or < 1/2 vertical height remains: consider low profile mandibular reconstruction plate
- If segmental mandibulectomy: consider microvascular osseous free tissue transfer (fibula, iliac crest, scapula, or scapular tip) or letting mandible swing (if lateral defect, patient edentulous or patient not candidate for reconstruction)
  - In patients with poor performance status or significant comorbidities with posterolateral defects, consider soft tissue reconstruction or no osseous reconstruction at all

Neck
- N0: perform level appropriate neck dissection based on location of primary tumor if concern for occult cervical metastases is > 20%
  - In patients with level IV disease, consider inclusion of level V in dissection
- N+: selective neck dissection with minimum of levels IA, IB, IIA, IIB, III, IV
  - Subsite specific general guidelines for N0 neck:
    - Oral tongue or floor of mouth
If depth < 4 mm: observe neck
If depth > 4 mm: selective neck dissection of levels IA, IB, IIA, III
  - Consider extended dissection to levels IV and V based on intraoperative findings
bilateral neck dissections if concern for bilateral spread based on primary tumor location (ie: central floor of mouth or tongue, tongue lesions crossing midline)
  - Lip
    - if T1 or T2: observe neck
    - T3 or T4: selective neck dissection of levels IA, IB, IIA, III
  - bilateral neck dissections if concern for bilateral spread based on primary tumor location

6.2 Chemotherapy

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

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
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
- 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)
- 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 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
  - >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

CONCURRENT RADIOTHERAPY + TARGETED THERAPY

- Cetuximab 400mg/m² loading dose week prior to radiotherapy, then 250mg/m² weekly concurrent with radiotherapy

SETTING:

- outpatient chemotherapy suite
o Pre-treatment Assessment:
  ▪ Bloodwork: CBC, lytes, creatinine, liver function
  ▪ Vital signs

o Pre-Medication / Hydration
  ▪ Diphenhydramine 50mg IV, 30-60 mins prior to each dose
  ▪ Dexamethasone 10mg IV, 30-60 mins prior to each dose

o 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
  o Consider for patients not suitable for high-dose cisplatin
  o SETTING:
    ▪ Out-patient chemotherapy suite
  o Pre-treatment Assessment:
    ▪ Bloodwork: CBC, lytes, creatinine, liver function, hepatitis B and C profile, weight, height and BSA.
  o 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:
• 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

  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 4 mg 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)
        o 1-1.4 x 10e9/L: consider delay for 1 week, or 75% dose reduction
        o <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
    ▪ Neuropathy 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 or 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
  o 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
- Post-surgical imaging of H&N and Thorax to rule out early recurrence

**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 review for pts with G-tube, or as clinically indicated)
    - Bloodwork prior to each cycle of chemotherapy, 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 nasoendoscopy
  - Imaging
    - CT head and neck at 10-12 weeks post-treatment
    - Other imaging as clinically indicated
  - Pharyngeal function (speech/swallow) as 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:
o refer to NECK DISSECTION policy above (Surgery, 6.1) for management of suspected / confirmed persistent regional disease
o RE-IRRADIATION: refer to guideline for re-treatment of pts with H&N malignancy for re-irradiation
  ▪ RT volumes
  ▪ Fractionation
  ▪ Use of concurrent Rx