



Provincial Head and Neck Cancer Treatment Guidelines

Approved at the Provincial Head and Neck Cancer Guideline Meeting
May 8, 2015

Clinical practice guidelines have been developed after multi-disciplinary consensus based on best available literature. As the name suggests, these are to be used as a guide only. These guidelines do not replace physician judgment which is based on multiple factors including, but not limited to, the clinical and social scenario, comorbidities, performance status, age, available resources and funding considerations. The Saskatchewan Cancer Agency disclaims all liability for the use of guidelines except as expressly permitted by the Agency. No portion of these guidelines may be copied, displayed for redistribution to third parties for commercial purposes or any non-permitted use without the prior written permission from the Agency.

Recommendations for drug treatment presented in the Cancer Agency guidelines for a cancer site may not reflect provincial cancer drug funding. Please refer to the current Saskatchewan Cancer Agency drug formulary at www.saskcancer.ca for information on cancer drug listing and funding.

Benefits and risk of the proposed should be discussed with patient.

Participating in clinical trials is encouraged when available. Involvement of a multidisciplinary team is strongly recommended.

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DIAGNOSIS AND WORK-UP

- Complete head and neck examination
- Biopsy
- Computed tomography (CT) with contrast and/or magnetic resonance imaging (MRI) with contrast of primary site and neck, as indicated Chest CT scan, if not included with other imaging
- Positron emission tomography-computed tomography (PET-CT), as indicated
- Examination under anesthesia with endoscopy, as indicated
- Preanesthesia studies
- Dental/prosthetic evaluation, including jaw imaging, as indicated
- Nutrition, speech and swallowing evaluation/therapy should be conducted by a registered dietician and a speech-language/swallowing service.

Staging is as per AJCC/UICC TNM Staging. 7th edition.

SYSTEMIC/CHEMOTHERAPY TREATMENTS

Patients with early stage I and II disease are generally treated with either radiation or surgery with good outcomes.

A. Definitive/radical Chemo-radiotherapy

The majority of patients with head and neck cancer present with locally advanced disease and require combined modality therapy using chemotherapy, radiation and/or surgery.

This concurrent chemoradiotherapy refers to the administration of chemotherapy in combination with radiation without upfront surgical resection. This is **definitive/radical chemo-radiotherapy**. Salvage surgery in this case is used in case of persistent disease after chemoradiotherapy. The meta-analysis in head and neck cancer showed an 8% absolute benefit with concurrent chemoradiotherapy compared to radiation therapy alone.

Cisplatin bolus at 100 mg/m² every three weeks x3 during radiation is used in patients with advanced disease. Cisplatin at this dose has many side effects including neuropathy, hearing loss, severe nausea / vomiting and renal dysfunction. Other regimen includes Carboplatin + infusional 5FU.

Weekly cetuximab in patients who cannot tolerate high dose cisplatin is used based on phase III study with cetuximab+ radiation.

Patients who are not fit enough to receive bolus cisplatin at q3 week dose may be evaluated for regimens like weekly cisplatin or weekly carboplatin and Paclitaxel. These regimens have not been studied in **recent** randomized phase III studies.

B. Post-operative Chemoradiotherapy

Used after surgical resection for patients with high risk recurrence. Post operative concurrent chemoradiotherapy has been tested in two phase III studies: RTOG-9501 and EORTC-22931. Both studies randomized patients with **high-risk** surgical-pathologic features after surgery to radiation therapy or radiation therapy plus cisplatin (100 mg/m² q3wk x 3 cycles).

High risk features were defined as follows: presence of positive margin, extra capsular spread outside the lymph nodes, lymphovascular invasion, perineural invasion and multiple positive lymph nodes. In RTOG-9501, chemoradiotherapy significantly reduced the risk of locoregional recurrence compared with radiation therapy alone. No benefit on overall survival was noted. In EORTC-22931, both progression-free survival and overall survival were significantly longer with chemoradiotherapy. The metastatic rate was 25% with radiation only, and 20% with combined therapy. Postoperative chemoradiotherapy was more effective than radiation therapy alone, but also more toxic.

A pooled analysis of data from both trials showed that two risk factors were associated with significant benefit from chemo-radiotherapy in both trials: extra-capsular extension and positive surgical margins. These two features are highly predictive of both local and distant failures. Current studies are exploring whether the addition of targeted therapy to concurrent chemoradiotherapy improves outcome.

Therefore if a patient has the following adverse risk features **after upfront surgery**:

- Extra-capsular spread or positive margin: **ChemoRT is recommended**
- Positive margin: if feasible, consider re-resection to achieve negative margins; if re-resection is not possible; ChemoRT advised.
- For pT3 or T4, level IV or V nodal disease from N2 or N3, Perineural invasion and/or vascular embolism: RT alone. ChemoRT may be considered, the decision should be based on clinical judgment and in discussion with the multidisciplinary group.

If the patient does not have the above adverse risk features proceed with follow-up and surveillance.

C. Induction Chemotherapy

Platinum +FU induction chemotherapy has been the standard regimen used in induction protocols for sometimes. Two randomized phase III trials added docetaxel to PF induction chemotherapy. Both studies showed a significant benefit with the three drug combination (TPF) when compared to PF

(Tax 323 and Tax 324)

In Tax 323 study 358 patients with SCCHN with previously untreated inoperable, locally advanced stages III and IV, and good performance status, received either docetaxel 75 mg/m² followed by cisplatin 75 mg/m² on day 1, followed by 5-fluorouracil 750 mg/m²/day as a continuous intravenous infusion on days 1-5 (TPF), or cisplatin 100 mg/m² on day 1, followed by 5-fluorouracil 1000 mg/m² /day as a continuous intravenous infusion on days 1-5 (PF). These regimens were administered every three weeks for 4 cycles. Four to 7 weeks after chemotherapy, patients whose disease had not progressed received radiotherapy. Radiation was delivered either with a conventional or an accelerated/hyperfractionated regimen (i.e. more than one fraction per day).

Surgical resection was allowed following chemotherapy, before or after radiotherapy. The trial's primary endpoint was progression-free-survival (PFS) that was defined as time from randomization to disease progression or death from any cause, whichever occurred first. Median PFS was significantly longer in the TPF arm (11.4 months) than in the PF arm (8.3 months). Median overall survival was significantly longer in the TPF arm (18.6 months) than in the PF arm (14.2 months).

Tax 324 included patients who had both operable and inoperable disease. 501 patients with previously untreated locally advanced SCCHN, and good performance status, received either docetaxel 75 mg/m² followed by cisplatin 100 mg/m² on day 1, followed by 5-FU 1000 mg/m²/day as a continuous intravenous infusion on days 1-4 (TPF) or cisplatin 100 mg/m² on day 1, followed by 5-FU 1000 mg/m² /day as a continuous infusion on days 1-5 (PF). These regimens were administered every 3 weeks for 3 cycles. All patients in both treatment arms who did not have progressive disease following induction chemotherapy (close to 80%) received 7 weeks of chemo-radiotherapy (CRT). During radiotherapy, carboplatin, area under the curve (AUC) of 1.5 was administered weekly as a 1-hour infusion for a maximum of 7 doses.

Surgery could be considered at anytime following completion of CRT. The majority of patients had locally advanced stage IV disease (84%). Overall survival was significantly prolonged with TPF compared to PF regimen (log-rank test, p=0.0058). The median survival was 70.6 months in the TPF group compared to 30.1 months in the PF group.

Summary:

- May allow time to optimize patient medical status; customization of RT dosing based on response to treatment; provides early treatment of distant micrometastatic disease
- However severe side effects of Induction CT may adversely affect compliance to subsequent concurrent CT/RT or choice of CT/RT regimen; It adds 2-4 months to treatment
- Clear long term advantage is not established. Important studies results awaited.

For present, risk-based TPF Chemotherapy can be discussed **for excellent** performance status patients with:

- Very locally advanced disease (eg, bulky, N2c, N2b, N3, low neck, dermal infiltration)
- Or Organ preservation strategy in patients with very locally advanced disease

D. Palliative Chemotherapy

1st line therapy:

- historically platinum-based doublet
- overall RR 30-40%
- median survival 6-9 months regardless of treatment
- randomized controlled trials fail to demonstrate clear improvement in OS with doublet chemo regimen compared to chemo with single agents

Active agents: Cisplatin, Carboplatin, 5-FU, Taxanes, Methotrexate, Cetuximab, Ifosfamide, Gemcitabine.

First line Cetuximab (anti EGFR antibody) with chemotherapy, phase III (**Extreme trial**) study, showed that the addition of cetuximab to platinum-5-fluorouracil is superior to platinum-5-fluorouracil alone.

Median survival was 7.4 months in the chemotherapy alone arm compared to 10.1 months for chemotherapy plus cetuximab arm ($p=0.036$). Approximately 60% of patients enrolled on this trial did not receive chemotherapy (chemo-naïve) as part of definitive therapy. The benefit appears to be more pronounced in those younger than age 65, in good performance status and in those received cisplatin-based treatment.

E. Follow-Up and Surveillance

- Head and neck examination (note that the ranges are based on risk of relapse, second primaries, treatment side effects, and toxicities):
 - Year 1, every 1 to 3 months
 - Year 2, every 2 to 6 months
 - Year 3–5, every 4 to 8 months
 - After 5 years, annually, as clinically indicated
- Annual thyroid-stimulating hormone (TSH) screening up to 5 years only for those patients that receive post-operative RT to the neck.
- Speech/swallowing assessment at 6 and 12 months post-RT; additional assessment and rehabilitation, as clinically indicated by a speech-language/swallowing therapist.
- Hearing evaluation and rehabilitation, as clinically indicated.
- Follow-up with a registered dietitian to evaluate nutritional status and until the patient achieves a nutritionally stable baseline•
- Routine hospital-based dental follow-up/rehabilitation and evaluation up to 3 years, specifically:
 - Half-way through treatment
 - At the end of treatment
 - 6 weeks post treatment
 - 2–3 months post treatment
 - 6 months post treatment
 - 12 months post treatment
 - Yearly for the next 2 years•
- Physiotherapy is indicated for all patients undergoing major head and neck resection during the first 3–6 months post-operation.

NASOPHARYNGEAL CANCER (NPC) EPIDEMIOLOGY

- Different subtypes:
 - **WHO type I (keratinizing, squamous cell carcinoma)** common in the non-endemic areas of the world and has a morelocoregional behavior.
 - **WHO type II (non-keratinizing carcinoma, differentiated) & WHO type III (non-keratinizing, undifferentiated)** predominant endemically in regions such as south China, north Africa and the far north hemisphere.
 - Not smoking related and has a higher propensity for distant metastases.
 - The typical lymphoepithelioid-type is associated with the non-keratinizing, subtype.

- Peak incidence is in the fourth and fifth decade of life, male:female ratio is 2.2:1.0. Geographic incidence varies greatly: in non-endemic regions incidence is <1/100,000.
- Associated with EBV infection. EBV DNA as well as anti-EBV antibodies are found in patients with NPC and have been used as tumor markers, although not routinely utilized.

NPC sometimes can be associated with HPV.

- While the TNM system is used for staging in the North America, an alternative – the Ho system – is commonly used in Asia. Differences between these systems need to be considered when the results of trials are compared.

Treatment:

- Because of anatomy and radiosensitivity, radiation is the major aspect of treatment.
- Concurrent chemotherapy (Cisplatin) during radiation improves survival. This is the current standard of care (RTOG 0099). The incremental benefit of adding adjuvant chemotherapy to concurrent chemoRT alone is debated.

A meta-analysis of available randomized trials shows a significant association between the timing of chemotherapy and overall survival ($p=0.006$), with the largest benefit associated with concurrent therapy

In 2012 a large phase III study comparing chemoRT to chemoRT + Adjuvant chemotherapy found no difference in survival between the two study arms. NCCN guidelines 2014 have been revised to reflect the results of this important phase III trial. Adjuvant Carboplatin based regimen has shown similar result in recent study but had short follow-up and wide confidence intervals .

Follow-Up:

- Physical exams:
 - every 1- 3 months (Year 1)
 - 2 - 4 months (Year 2)
 - 4 - 6 months (Years 3-5)
 - and every 6 -12 months thereafter.
- Imaging of the primary site and neck within six months of the completions of treatment. Once treatment is completed and the patient is felt to be disease free, routine imaging of the primary site and neck are **not routinely indicated** in the absence of suspicious signs or symptoms.
- Thyroid stimulating hormone test every 6-12 months (if neck radiation was administered)
- Chest imaging “as clinically indicated”

For chemo regimen and doses, please refer to SCA formulary and preprinted protocols.

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