

OROPHARYNGEAL CANCER TREATMENT

Effective Date: February 2019

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The recommendations contained in this guideline are a consensus of the Alberta Provincial Head and Neck Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care. The Tumour Team recognizes that the treatment of oropharyngeal cancer is rapidly evolving and as such there will be some variation in the nuances of treatment.

All cancer drugs described in the guidelines are funded in accordance with the Outpatient Cancer Drug Benefit Program, at no charge, to eligible residents of Alberta, unless otherwise explicitly stated. For a complete list of funded drugs, specific indications, and approved prescribers, please refer to the [Outpatient Cancer Drug Benefit Program Master List](#).

Participation of members of the Alberta Provincial Head and Neck Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Head and Neck Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

BACKGROUND

The impact of oropharyngeal cancer on population health in Canada is difficult to assess because incidence rates are largely described in combination with other head and neck subsites. The oropharynx is the part of the pharynx that is posterior to the oral cavity, between the nasopharynx and the hypopharynx. The subsites of the oropharynx are the base of tongue, tonsillar region, soft palate, and pharyngeal wall. Squamous cell carcinomas account for the vast majority (>90%) of oropharyngeal cancers.¹ Patients with oropharyngeal cancer are often asymptomatic until the tumour reaches a significant size or metastasizes to a lymph node in the neck. Approximately 70% of patients present to cancer specialists at an advanced stage (stage III or IV).² Similar to other cancers of the head and neck, patients with a history of overusing tobacco and/or alcohol are at increased risk for the development of oropharyngeal cancer. Human papillomavirus (HPV) is also a well-recognized risk factor and likely underlies the worldwide increase in the incidence of oropharyngeal cancer. In Alberta, we have also experienced an increasing incidence of HPV-related oropharyngeal cancer.³ HPV16 accounts for 90-95% of HPV-positive oropharyngeal cancers.⁴ Although improved survival rates have been documented in HPV-positive compared with HPV-negative patients,⁵ current treatment approaches are similar. The treatment options for oropharyngeal cancer include surgery, radiation, and chemotherapy. Depending on the tumour stage, subsite, and patient performance status, these treatments can be offered as single modality or combined-modality. Molecular-targeted therapies are emerging as well and will be incorporated into the treatment guidelines as evidence becomes available.

The purpose of this guideline is to outline treatment recommendations for patients with oropharyngeal cancer in Alberta. These guidelines should be applied in the context of the recommendations outlined in Alberta Health Services, CancerControl Alberta guideline, [The Organization and Delivery of Healthcare Services for Head and Neck Cancer Patients \(HN-001\)](#).

GUIDELINE QUESTIONS

1. What diagnostic investigations and baseline assessments are recommended for patients with suspected or confirmed oropharyngeal cancer?
2. What are the recommended treatment options for early (stage I and II) oropharyngeal cancer?
3. What are the recommended treatment options for locally advanced (stage III and IV) oropharyngeal cancer?
4. What are the recommended treatment options for metastatic and recurrent oropharyngeal cancer?
5. What are the recommended rehabilitation and follow-up strategies post-treatment for oropharyngeal cancer?

DEVELOPMENT AND REVISION HISTORY

The Alberta Provincial Head and Neck Tumour Team used the following steps to develop this guideline:

1. The Alberta Provincial Head and Neck Tumour Team Executive members individually reviewed the results of an environmental scan of published clinical practice guidelines (CPGs) related to the treatment of oropharyngeal cancer.
2. Based on this review, the Executive supported adapting the National Comprehensive Cancer Care (NCCN) guidelines.⁶

3. At a face-to-face meeting in September 2014 the Executive reviewed NCCN's recommendations for the treatment of oropharyngeal cancer and made revisions based on consideration of context to ensure relevance for local practice. Subsequent Executive teleconferences were needed to fine tune the recommendations.
4. The draft recommendations were then sent out to all members of the Provincial Head and Neck Tumour Team (approximately 150 individuals from multiple disciplines) using a web-based survey tool. Respondents were asked to review the recommendations, indicate their level of agreement with each recommendation, and provide comments on the usefulness of the recommendations, and suggestions for improvement. All responses were anonymous. Response rate was 34%.
5. The Executive individually reviewed the survey results and then discussed the proposed revisions to the recommendations during a teleconference in June 2015.
6. The guideline was reviewed by the Executive in August 2018, at which time minor edits were incorporated and approved by the Tumour Team. The Tumour Team recognizes that the treatment of oropharyngeal cancer is rapidly evolving, and a comprehensive update of this guideline will be necessary over the next 1-2 years.

SEARCH STRATEGY

The National Guideline Clearinghouse (NGC, Agency for Healthcare Research and Quality, www.guideline.gov) was searched for clinical practice guidelines published between 2012 and 2015 related to the treatment of oropharyngeal cancer, and the webpages of well-recognized cancer guideline developers was hand-searched to ensure no clinical practice guidelines had been missed. A review of the primary literature was conducted using PubMed and the Cochrane Database of Systematic Reviews; the full literature search strategy and results are included in Appendix A.

TARGET POPULATION

The recommendations outlined in this guideline are intended for adults over the age of 18 years with oropharyngeal cancer. Different principles may apply to pediatric patients.

RECOMMENDATIONS

Caring for patients with oropharyngeal cancer is complex and requires the expertise of many specialists as outlined in the guideline, [HN-001](#). Whenever possible, patients with oropharyngeal cancer should be considered for eligibility in ongoing clinical trials, and every case should be presented at a multidisciplinary tumour board. Tumour board review utilizes the expertise of a variety of specialists who draw on their own experiences with similar patient cases and current treatment approaches based on the literature.

With no large randomized control trials comparing surgical versus non-surgical treatments for patients with oropharyngeal cancer, there is a lack of high level evidence as to the optimum management strategy. However, there is agreement that the goals of treatment include maximizing loco-regional control, survival, functional outcomes, cosmesis, quality of life, and cost-effectiveness. Questions about cost-effectiveness and comparative value of treatments are beyond the scope of this clinical practice guideline.

Diagnostic Investigations and Baseline Assessments

1. The following diagnostic investigations are recommended for patients with suspected oropharyngeal cancer:
 - Complete head and neck examination,
 - Neck and chest computed tomography (CT), or, depending on the clinical scenario, positron emission tomography (PET)/CT,
 - Biopsy,
 - Examination under anesthesia with endoscopy, if indicated, and
 - HPV status using immunohistochemical (IHC) staining for p16.⁷⁻¹⁰
2. The following baseline assessments are recommended for patients with confirmed oropharyngeal cancer to establish a clear supportive care plan for the patient's treatment journey:
 - Nutrition, speech and swallowing evaluation should be conducted by a registered dietician and a speech-language/swallowing therapist as described in [HN-001](#); indicated for patients with significant weight loss (more than 10% body weight), and/or difficulty with speech/swallowing, and/or for patients whose treatment is likely to affect speech/swallowing, and¹¹⁻¹⁸
 - Dental/prosthetic evaluation, including dental and jaw imaging.^{19,20}

Treatment Options

Patient participation in clinical trials is recommended. All cases should be presented and discussed at a multidisciplinary tumour board to decide the best treatment option for each patient. Treatment should begin within four weeks of being ready to treat. Staging is based on the AJCC 7th Edition TNM staging system. With the publication of the AJCC 8th Edition TNM staging system the Alberta Head and Neck Cancer Provincial Tumour team is in the process of updating the current treatment guidelines with current best available evidence.

Early-Stage (T1-2, N0-1)

3. Single modality treatment with either surgery or radiotherapy (RT) is recommended for most patients with T1-2, N0-1 disease.²¹⁻²⁴ A decision regarding the most appropriate treatment should be guided by an evaluation of potential functional deficits post-treatment, as well as patient preference, patient's physical condition, potential morbidity including impact on functional outcomes and cosmesis, patient's quality of life, and length of hospital stay.
4. Treatment of the neck is recommended for all patients with early-stage disease.^{25,26} Bilateral neck treatment is required for tumours involving midline structures with bilateral lymphatic drainage.

Surgery:

- For patients with no adverse risk features on pathology, no further treatment is required.
- Surgery to remove the primary tumour could be via an open approach or a transoral approach as deemed appropriate by the treating surgeon(s), and based on local expertise and resources.
- For patients with positive surgical margins and/or extracapsular spread, chemoRT is indicated ≤6 weeks after surgery.
- For patients with positive surgical margins alone, re-resection is the preferred treatment. If unresectable, RT or chemoRT is recommended.

- If other adverse risk features are present patients may be managed with RT. Clinical judgment should be used if consideration of adding chemotherapy to RT exists.

Radiotherapy:

- The recommended RT dose is 66–70 Gy.
- In the case of residual disease, treatment with salvage surgery is recommended.

Radiotherapy plus Systemic Therapy:

- In the case of residual disease, treatment with salvage surgery is recommended.

Please click [here](#) to view the early-stage (T1-2, N0-1) treatment algorithm.

Locally Advanced Stage (T3-4a, N0-1) Treatment Options

5. Multimodality treatment with either surgery followed by RT or chemoRT, or concurrent chemoRT is recommended for patients with T3-4a, N0-1 disease. A decision regarding the most appropriate treatment should be guided by an evaluation of potential functional deficits post-treatment, as well as patient preference, patient's physical condition, potential morbidity including impact on functional outcomes and cosmesis, patient's quality of life, and length of hospital stay.

Surgery Followed by Radiotherapy or ChemoRT:

- Most patients with pT3-4a, N0-1 disease without additional adverse risk factors require post-op RT alone.
- For patients with positive margins and/or extracapsular spread, chemoRT is indicated ≤6 weeks after surgery.
- Patients with good performance status, especially in the presence of other risk factors (e.g., high grade, pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, and lymphovascular invasion) may be considered for chemoRT.
- The recommended postoperative RT dose is 60–66 Gy.
- The recommended postoperative chemoRT regimen is concurrent single-agent cisplatin at 100 mg/m² every 3 weeks.²⁷⁻³⁰

Concurrent ChemoRT:

- The recommended RT dose is 66–70 Gy.
- Single-agent cisplatin is the preferred chemotherapeutic agent.^{31,32} Weekly cetuximab is a reasonable alternative to use with concurrent radiation in patients deemed cisplatin-intolerant.³³
- Patients with a complete clinical response may be observed. All patients with an incomplete response to treatment should be re-reviewed by the multidisciplinary tumour board to discuss indications for salvage surgery.

Please click [here](#) to view the locally advanced (T3-4a, N0-1) stage treatment algorithm.

Locally Advanced Stage (Any T, N2-3) Treatment Options

6. Multimodality treatment with either surgery followed by RT or chemoRT, or concurrent chemoRT is recommended for patients with any T, N2-3 disease. A decision regarding the most appropriate treatment should be guided by an evaluation of potential functional deficits post-treatment, as well as

patient preference, patient's physical condition, potential morbidity including impact on functional outcomes and cosmesis, patient's quality of life, and length of hospital stay.

Surgery Followed by Radiotherapy or ChemoRT:

- For patients with positive margins and/or extracapsular spread and with a good performance status, chemoRT is indicated ≤ 6 weeks after surgery.
- RT is indicated for patients with other risk factors, including high grade, pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, and lymphovascular invasion.
- The recommended postoperative RT dose is 60–66 Gy.
- The recommended postoperative chemoRT regimen is concurrent single-agent cisplatin at 100 mg/m² every 3 weeks.²⁷⁻³⁰

Concurrent ChemoRT:

- The recommended RT dose is 66–70 Gy.
- Single-agent cisplatin is the preferred chemotherapeutic agent.^{31,32} Weekly cetuximab is a reasonable alternative to use with concurrent radiation in patients deemed cisplatin-intolerant.³³
- Patients with a complete clinical response at the primary site, as well as the neck should be seen in clinic for an assessment 4–8 weeks post treatment. Consider CT and/or MRI with contrast, or PET/CT scan to assess extent of the disease or distant metastases if persistent disease or progression is suspected. If diagnosis is confirmed or progression is evident, proceed with neck dissection.
- Patients with residual disease at the primary site should be presented at multidisciplinary tumour board to discuss salvage treatment options.
- Neck dissection is also recommended for patients with a complete clinical response at the primary site, but an incomplete response in the neck.

Please click [here](#) to view the locally advanced (Any T, N2-3) stage treatment algorithm.

Very Advanced Stage (T4b, and N, or unresectable nodal disease, or unfit for surgery) Treatment Options

7. Patients should be managed on an individual basis with input from members of the multidisciplinary tumour board.

Rehabilitation and Follow-up Strategies

8. The subsequent follow-up schedules are recommended post-treatment to detect recurrences, distant metastases, second primary malignancies, or treatment complications:^{34,35}
 - Head and neck examination (note that the ranges are based on risk of relapse, second primaries, treatment sequelae, and toxicities):
 - Year 1, every 1–3 months
 - Year 2, every 2–6 months
 - Year 3–5, every 4–8 months
 - >5 years, annually, as clinically indicated
 - Annual thyroid-stimulating hormone screening up to 5 years; indicated for patients that receive RT to the neck³⁶⁻³⁸
 - Routine dental evaluations:^{19,20}

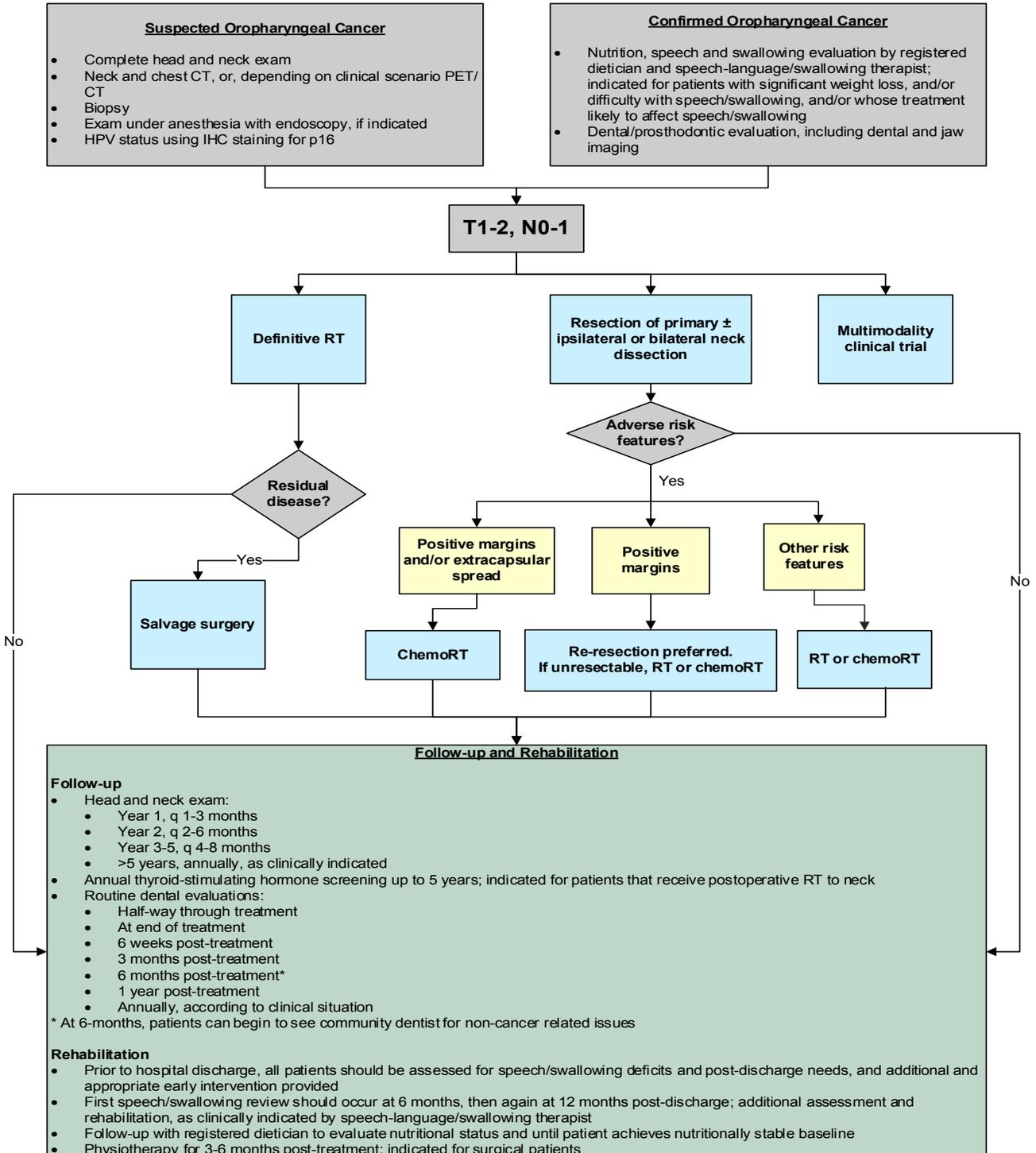
- Half-way through treatment
- At the end of treatment
- 6 weeks post-treatment
- 3 months post-treatment
- 6 months post-treatment*
- 1 year post-treatment
- Annually, according to clinical situation

* At 6 months, patients can begin to see community dentist for non-cancer related issues

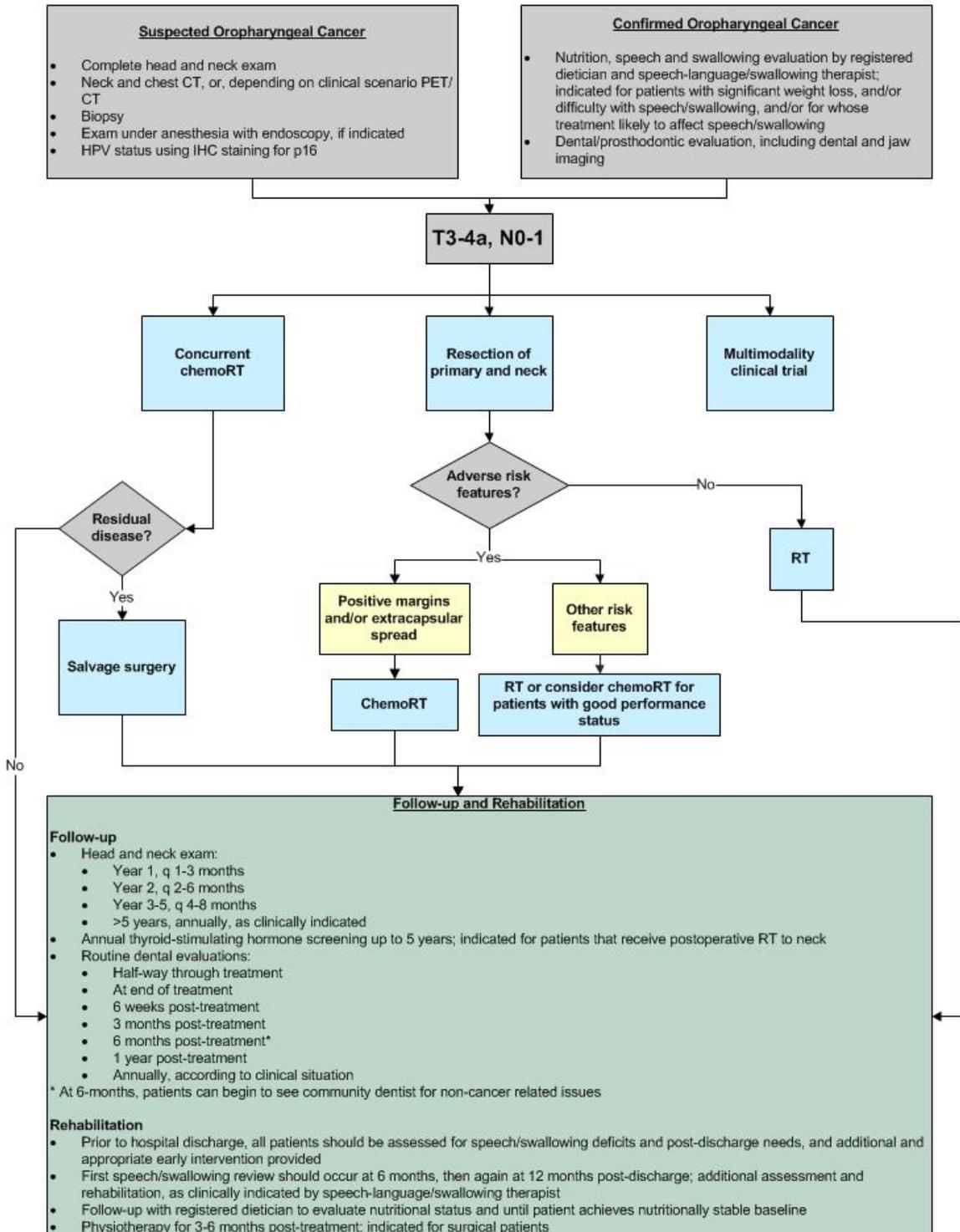
9. The following rehabilitation strategies are recommended post-treatment to aid the patient in achieving a stable functional baseline:
- Prior to hospital discharge, all patients should be assessed for speech/swallowing deficits and post-discharge needs, and additional and appropriate early intervention provided,¹⁶⁻¹⁸
 - The first speech/swallowing review should occur at 6 months, then again at 12 months post-discharge; additional assessment and rehabilitation, as clinically indicated by a speech-language/swallowing therapist,
 - Follow-up with a registered dietician to evaluate nutritional status and until the patient achieves a nutritionally stable baseline, and
 - Physiotherapy for 3–6 months post-treatment; indicated for surgical patients.

TREATMENT ALGORITHMS

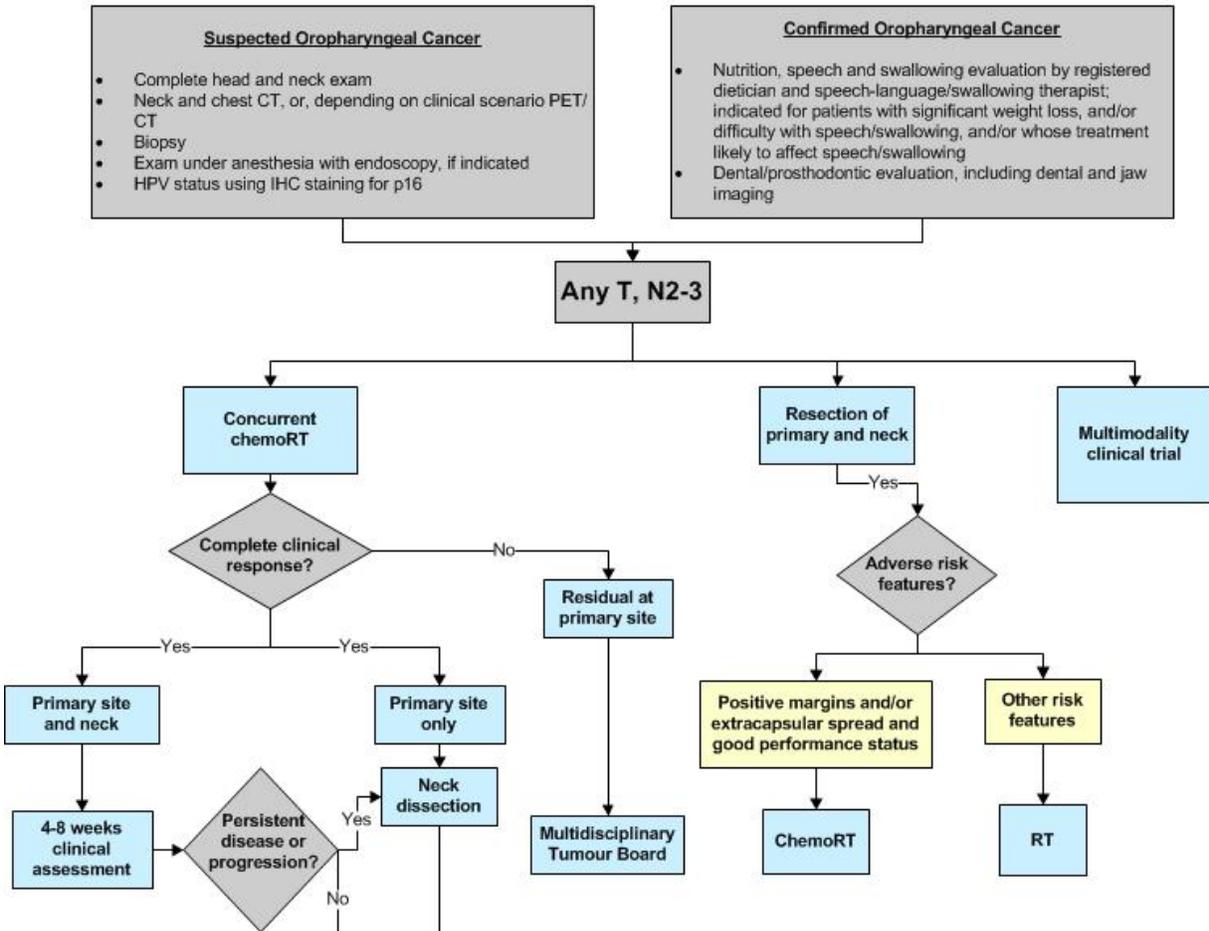
Patient participation in clinical trials is recommended. For standard treatment, all cases should be presented and discussed at a multidisciplinary tumour board to decide the best treatment option for each patient.



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Follow-up and Rehabilitation

Follow-up

- Head and neck exam:
 - Year 1, q 1-3 months
 - Year 2, q 2-6 months
 - Year 3-5, q 4-8 months
 - >5 years, annually, as clinically indicated
- Annual thyroid-stimulating hormone screening up to 5 years; indicated for patients that receive postoperative RT to neck
- Routine dental evaluations:
 - Half-way through treatment
 - At end of treatment
 - 6 weeks post-treatment
 - 3 months post-treatment
 - 6 months post-treatment*
 - 1 year post-treatment
 - Annually, according to clinical situation

* At 6-months, patients can begin to see community dentist for non-cancer related issues.

Rehabilitation

- Prior to hospital discharge, all patients should be assessed for speech/swallowing deficits and post-discharge needs, and additional and appropriate early intervention provided
- First speech/swallowing review should occur at 6 months, then again at 12 months post-discharge; additional assessment and rehabilitation, as clinically indicated by speech-language/swallowing therapist
- Follow-up with registered dietician to evaluate nutritional status and until patient achieves nutritionally stable baseline
- Physiotherapy for 3-6 months post-treatment; indicated for surgical patients

GLOSSARY OF ABBREVIATIONS

Acronym	Description
CPG	clinical practice guideline
CT	computed tomography
HPV	human papillomavirus
IHC	immunohistochemistry
NCCN	National Comprehensive Cancer Care
PET	positron emission tomography
NGC	National Guideline Clearinghouse
RT	radiotherapy

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2020. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

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APPENDIX A: Literature Search Strategy

Date of Literature Review: March 26, 2015

Published Guidelines:

- To identify existing treatment guidelines, the National Guideline Clearinghouse directory was searched in addition to prominent guideline developer websites.
- Limits: January 1, 2012 to March 26, 2015.
- Results: 3 published guidelines from the NCCN (2014), NICE (2014), and Cancer Care Ontario (2013) were identified.

PubMed:

- Search strategy: ("oropharyngeal neoplasms"[MeSH Terms] OR ("oropharyngeal"[All Fields] AND "neoplasms"[All Fields]) OR "oropharyngeal neoplasms"[All Fields] OR ("oropharyngeal"[All Fields] AND "cancer"[All Fields]) OR "oropharyngeal cancer"[All Fields]) AND ((Clinical Trial[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] OR Controlled Clinical Trial[ptyp] OR Multicenter Study[ptyp] OR Randomized Controlled Trial[ptyp]) AND "humans"[MeSH Terms] AND English[lang] AND "adult"[MeSH Terms])
- Results: 387 articles identified; 35 articles selected where >50% of patients w primary tumour of oropharyngeal cancer AND ≥50 patients
- Reference lists of selected articles were scanned for relevant literature

Cochrane Database of Systematic Reviews

- Search: oropharyngeal cancer
- Limits: none
- Results: 9 reviews identified, 4 selected