Guideline Resource Unit
guru@ahs.ca

Laryngeal Cancer

Effective Date: August, 2022

Cancer Care Alberta

Clinical Practice Guideline HN-009 – Version 1
www.ahs.ca/guru

Background

Laryngeal cancers in Alberta remain one of the more common subsites among head and neck cancers. Unfortunately, there has only been modest improvement in long-term survival of laryngeal cancer. The improvement is largely attributable to reduced smoking rates as opposed to changes in treatment[1]. Approximately 1150 laryngeal cancers occur annually in Canada including 85 among Albertans. Men are disproportionately affected with more than seven laryngeal cancers among men for every female affected. The overall incidence has declined over time due to public health measures and associated smoking cessation. It is noted that a proportion of laryngeal cancers develop among non-smokers. Additional risk factors include excessive alcohol consumption and specific occupational exposures (e.g., hardwood dust, asbestos, polycyclic hydrocarbons). The role of gastroesophageal reflux and human papillomavirus remain debatable.

Squamous cell carcinomas account for 95% of laryngeal cancers. Less common histological types include sarcomas, adenocarcinomas, and neuroendocrine tumours. Laryngeal cancers are organized according to their site of origin within the larynx compromised of the supraglottis, glottis, and subglottis. The glottis (vocal folds) represents the most common laryngeal cancer site. Due to the early effect on voice, most glottic laryngeal cancers present as early-stage lesions. Squamous cell cancers are thought to develop as premalignant or dysplastic lesions that progress through stages of increasing atypia into invasive malignancies. Thus, timely assessment of patients with persistent voice change and associated risk factors for laryngeal cancer is critical.

Laryngeal cancers are treated by surgery, radiotherapy, chemotherapy, or a combination of modalities depending on tumour stage, location, and patient factors. Determining the degree of local invasion, and presence of regional and distant spread are essential during the workup of a laryngeal cancer patient to determine optimal treatment. This includes careful clinical examination and radiologic imaging. Laryngeal cancer is staged according to the tumour node metastasis (TNM) system. For more information on the TNM classifications, along with anatomic stage/prognostic groups, please refer to Appendix A.

Development and Revision History

This guideline was developed to outline treatment recommendations for patients with laryngeal cancer. These guidelines should be applied in the context of the recommendations outlined in Alberta Health Services, Cancer Control Alberta guideline, The Organization and Delivery of Healthcare Services for Head and Neck Cancer Patients. The 8th edition of the AJCC staging system has been used for this guideline[2].

Guideline Questions

1. What diagnostic and baseline investigations are recommended for patients with suspected or confirmed laryngeal cancer?

2. What are the standard pathology reporting requirements and elements that include reporting of margins?
3. What are the recommended treatment options for early glottic, advanced glottic and supraglottic cancer? What is the appropriate dosing and fractionation for radiotherapy?
4. What are treatment recommendations for recurrent, locally extensive, or metastatic laryngeal cancer?
5. What are the recommended roles of Speech Language Pathology (SLP) in pre-treatment assessment and management of acute and late effects of laryngeal cancer?
6. What are the competencies for allied health professionals (e.g. SLP, respiratory therapy) in the management of laryngectomy patients?

Search Strategy

PubMED, MEDLINE and Cochrane Database of Systematic Reviews were searched from 2000 to December 2020 for literature on the treatment of laryngeal cancer. Results were limited to phase III clinical trials, comparative studies, controlled clinical trials, guidelines, meta-analyses, multicenter studies, practice guidelines, randomized controlled trials and systematic reviews involving human subjects (19+ years) and published in English. Although phase II studies may be referenced in the discussion section, only phase III randomized studies and meta-analyses were considered for the literature search and review.

The ECRI Guidelines Trust ® and Canadian Partnership Against Cancer Guidelines Database were also searched from 2008 to December 2020 for guidelines on laryngeal cancer.

Target Population

The following recommendations apply to adult cancer patients with laryngeal cancer. Different principles may apply to pediatric patients.

Recommendations: Glottic Larynx [3, 4]

Early and advanced glottic cancers have very different treatment approach and outcomes. Early glottic carcinoma has very low propensity for regional lymph node involvement, therefore, treatment is targeted to the primary site. Definitive surgery (e.g. transoral laser microsurgery (TLM) or open partial laryngectomy) or radiation are both treatment options with comparable oncologic and functional outcomes, and should be discussed with patients so the optimum treatment decision can be made. Higher risks of recurrence are associated with progressively more advanced primary tumour[5]

I. Diagnosis and Baseline Investigations

Patient with laryngeal cancer benefit from tailored baseline investigations based on subsite involved, staging and clinical presentation. The following outline makes recommendations by subsite and stage.

Glottic Dysplastic Lesions or Carcinoma In Situ:

- Clinically, it may be difficult to differentiate a dysplastic lesion from early carcinoma
- Complete head and neck examination (consistent with guideline HN-008) with in-office laryngoscopy
- Incisional or excisional biopsy, ideally in the operating room (See Appendix B)

Early Glottic Cancer (T1 to T2, NO): *(Level of Evidence II, Strength of Recommendation B)*[2, 3]

- Complete head and neck examination (consistent with guideline HN-008) with in-office laryngoscopy
- Incisional or excisional biopsy, ideally in the operating room as this also allows for full assessment of tumour extent for staging (See Appendix B)
- Consideration for baseline assessment of voice and swallowing function, and counseling regarding potential effects of treatment options on voice, swallowing, and quality of life.
- T1a lesions rarely require imaging if fully assessed endoscopically
- Imaging can be considered to assess extent of disease and may including CT neck or MRI neck; imaging is recommended for clinically T1b tumors and bulky T2 with potential paraglottic involvement[6]
- Consider baseline video-stroboscopy
- Pre-treatment SLP evaluation is not mandatory (see “Role of Speech Language Pathology”)

Advanced Glottic Cancer (T3 or T4, or TxN1-3): *(Level of Evidence II, Strength of Recommendation B)*[3]

- Complete head and neck examination (consistent with guideline HN-008) with in-office laryngoscopy
- Incisional or excisional biopsy, ideally in the operating room to determine extent of tumor; (see Appendix B)
- Cross-sectional imaging including computed tomography (CT) of the neck and chest, or, depending on the clinical scenario, positron emission tomography (PET)/CT
- All patients should undergo a pre-treatment baseline assessment including:
    - Voice and swallowing evaluation by speech language pathology (see “Role of Speech Language and Pathology”)
    - Dental evaluation
    - Nutrition evaluation by a registered dietician to provide pre-treatment education and counselling
- Smoking cessation strategies should be discussed with patients, if applicable

II. Biopsy/Pathologic Reporting of Biopsy *(Level of Evidence III Strength of Recommendation C)*[2, 7, 8]

- A clinically suspected diagnosis of malignancy should be confirmed by operative biopsy or, if experience and equipment allows, in-office biopsy
- Excisional biopsy is appropriate in select patients (e.g. well visualized, unilateral mid-cord lesions)
- Laryngeal biopsies should be submitted with proper handling, orientation, labelling, and processing (See Appendix B)
- Adequate biopsies must include sufficient depth to assess invasion
- Expertise in laryngeal histopathology and head and neck pathology is needed to assess laryngeal biopsies and oncologic specimens
- p16/HPV testing of laryngeal cancers should not routinely be performed
- Please see Appendix B for additional details

III. Treatment Options

Cases should be presented and discussed at a multidisciplinary tumour board after a cancer diagnosis is established to decide the best treatment option for each patient. Treatment should begin within four weeks of being ready to treat (See HN-001). Staging is based on the AJCC 8th Edition TNM staging system.

Early Glottic Cancer

Table 1. Summary of Treatment Options for Early Glottic Cancer *(Level of Evidence I Strength of Recommendation A)*

***CIS*:** transoral laser surgery is preferred

T1 – T2, N0: Transoral laser surgery or open partial laryngectomy or radiation

- **T1a:** Transoral laser microsurgery is preferred
- **T2:** radiation is preferred
- Post-operative radiation is considered for positive margins, gross residual disease not amenable to re-resection

Surgery:

- Patients with T1 or T2 laryngeal cancer can be treated by either radiation therapy or surgery (e.g. transoral laser microsurgery or open partial laryngectomy) [9, 10]
- Surgery should be offered in centers where expertise and equipment enabling this approach are readily available

- CIS and T1a glottic cancer:
    - Transoral laser microsurgery is preferred if adequate resection margins can be obtained and functional outcomes are expected to be comparable to that of radiation therapy[10, 11].
    - For patients with positive surgical margins, re-resection can be considered but should be reviewed at a multidisciplinary tumour board. If unresectable, RT is recommended.
- T1b glottic cancer:
    - Transoral laser microsurgery (TLM), open partial laryngectomy, or radiation therapy[3]
- Open partial laryngectomy may be a surgical option for specific cases of T1/T2 glottic cancer with acceptable oncologic outcomes and functional preservation[2, 12].

Radiotherapy: *(Level of Evidence II Strength of Recommendation B)[3]*

Early-stage T1N0: [1]

- The recommended RT dose is 63 Gy (2.25 Gy/fraction) to 66 Gy (2.0 Gy/fraction) low dose fraction
- Hyper-fractionation is not recommended

Early-stage T2N0:[13]

- T2 glottic cancer:
    - Radiation therapy is recommended for patients with T2 glottic cancer.
- The recommended RT dose is 65.25 Gy (2.25 Gy/fraction) to 70 Gy (2.0 Gy/fraction)
- Altered fractionation with dose per fraction >2 Gy per day is also acceptable in addition to standard fractionation.

Follow-up and Rehabilitation:[2, 3]

- Patients should be followed a minimum of five years with a prolonged follow-up for selected patients (e.g. those with ongoing rehabilitative needs)
- Head and neck examination with laryngoscopy (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 for at least 5 years for patients that receive RT to the neck
- Please see “Role of Speech Language Pathology” and Appendix C

Advanced Glottic Cancer[3, 4, 12]

Advanced glottic tumours have significant functional impacts on airway, voice, and swallowing. There is also increased risk of nodal metastasis.

Table 2. Summary of Treatment Options for Advanced Glottic Cancer *(Level of Evidence II Strength of Recommendation B)*

T3Nx : RT + chemotherapy, salvage surgery for residual or recurrence, OR total laryngectomy with neck dissection. • Recommend: T3 tumours with bulky or transglottic disease may be considered for total laryngectomy with neck dissection. • Post-operative radiation is recommended in patients with adverse features **T4aNx:** Total laryngectomy ± Chemoradiotherapy

Surgery: *(Level of Evidence II Strength of Recommendation B)*

- Patients with bulky T3 and T4 disease, and those with poor pre-treatment laryngeal function may have improved survival and quality of life with upfront total laryngectomy[14].
- If surgery is performed, elective neck dissection is recommended for T3/T4 glottic carcinoma patients. [15, 16]
- Primary surgical voice restoration should be offered to all patients undergoing laryngectomy.
    - Tracheo-Esophageal-Puncture [TEP] with cricopharyngeal myotomy is the procedure of choice for voice rehabilitation among patients undergoing primary total laryngectomy and should be considered at the time of surgery[6]
    - Patient specific factors may necessitate a secondary TEP placement.
- Very select T3 tumors are appropriate for open partial laryngectomy
    - e.g. at least one cricoarytenoid unit can be preserved with surgery
- In clinically negative neck (cN0), elective management of the bilateral necks, including at least lymph node levels II, III and IV is necessary.
- In the presence of clinically or radiographically suspicious nodal involvement, therapeutic neck management is necessary.

Radiotherapy: *(Level of Evidence II Strength of Recommendation B)[3]*

- The recommended RT dose for primary treatment is 63 Gy (2.25 Gy/fraction) to 70 Gy (2.0 Gy/fraction) when given for curative intent in combination with chemotherapy.

- Post-operative radiation is recommended for positive margins, subglottic tumor extension, poorly differentiated disease[17]. The recommended RT dose for post-operative radiation is 60 (2 Gy/fraction) to 66 Gy (2.0 Gy/fraction).

Systemic Therapy Combined with Radiotherapy for Curative-Intent HNSCC[1]:

Standard chemotherapy regimens include:

- Cisplatin (100 mg / m2) on days 1, 21, 43 when combined with radiation
- Alternative cisplatin delivery schedule daily (6mg/m2), weekly (40mg/m2) or cetuximab (400/250 mg/m2) could be considered for the patients in which bolus cisplatin (100 mg/m2) would be contraindicated or poorly tolerated[13].
- Induction chemotherapy (i.e. TPF) is an option for individuals who otherwise would require total laryngectomy, however based on the results of the RTOG 91-11 demonstrating improved laryngeal preservation rates with concurrent administration, induction therapy is not preferred[18].

Very Advanced Stage Glottic Cancer *(Level of Evidence III Strength of Recommendation C)*

- This includes patients with T4bNx, unresectable nodal disease, or are unfit for surgery
- Patients should be managed on an individual basis with input from members of the multidisciplinary tumour board.
- In patients with unresectable disease, palliative chemotherapy or immunotherapy may be considered. See also “Palliative treatment recommendation” section.

IV. Follow-up and Rehabilitation[3]

- Patients should be followed a minimum of five years with a prolonged follow-up for selected patients (e.g. those with ongoing rehabilitative needs)
- Head and neck examination with laryngoscopy (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 neck
- Annual Chest X-ray
- Please see “Role of Speech Language Pathology” and Appendix C

Recommendations: SupraGlottic Larynx

The supraglottis has rich lymphatic supply and the risk of nodal metastasis is high even for T1 and T2 cancers. This fact is reflected in the recommended baseline investigations and treatment options. In many cases, supraglottic tumours present in a more advanced stage than glottic cancers due to the absence of voice change and later symptom onset.

I. Baseline Evaluations[3, 12] *(Level of Evidence III Strength of Recommendation B)*

- Complete head and neck examination (consistent with guideline HN-008) with in-office laryngoscopy
- Incisional or excisional biopsy, ideally in the operating room to determine extent of tumor
- Cross-sectional imaging including computed tomography (CT) of the neck and chest, or, depending on the clinical scenario, positron emission tomography (PET)/CT
- All patients should undergo a pre-treatment baseline assessment including:
    - Voice and swallowing evaluation by speech language pathology (see “Role of Speech Language and Pathology”)
    - Dental evaluation
    - Nutrition evaluation by a registered dietician to provide pre-treatment education and counselling
- Smoking cessation strategies should be discussed with patients, if applicable

II. Treatment

Table 3. Summary of Treatment Options for Supraglottic Cancer *(Level of Evidence II Strength of Recommendation B)*

T1 – T2, N0-1: open partial laryngectomy or transoral surgery or primary radiation **T3,Nx :** Concurrent chemoradiotherapy or total laryngectomy due to dysfunctional larynx and Post-operative RT **T4aNx:** Total laryngectomy and Post-operative RT or concurrent chemoradiotherapy

Surgery: *(Level of Evidence II Strength of Recommendation B)*

- Conservative laryngeal surgery (open partial laryngectomy or laser/robotic transoral laryngeal surgery) is recommended primarily for patients with T1/T2 supraglottic cancer[19].
    - Nodal disease (occult or clinically apparent) is common in T1/T2 tumors and thus treatment of the neck concurrently is recommended for clinical N0 supraglottic tumors.

- The preferred treatment for T4 supraglottic tumours is total laryngectomy with total thyroidectomy or ipsilateral when possible and (bilateral) neck dissection, followed by adjuvant treatment.
- Select T3 tumours may require total laryngectomy due to expectation of poor functional outcomes if treated non-surgically.
- For selected patients with T4 tumours who decline surgery, recommendation is concurrent chemoradiation.

Radiotherapy: ***(Level of Evidence II Strength of Recommendation B)***[3]

- The recommended RT dose for primary treatment is 66 Gy (2.0 gy/fraction) to 70 Gy (2.2 gy/fraction) for primary radiation with curative intent.
- Total doses of 66-70 Gy are recommended when combined with chemotherapy for curative intent.
- The recommended RT dose for post-operative is 60 (2 Gy/fraction) to 66 Gy (2.0 Gy/fraction).

Systemic Therapy Combined with Radiotherapy for Curative-Intent HNSCC*: (Level of Evidence I Strength of Recommendation A)*

Standard chemotherapy regimens include:

- Cisplatin (100 mg/m^2) on days 1, 21, 43 when combined with radiation.
- Alternative cisplatin delivery schedule daily (6mg/m^2), weekly (40mg/m^2) OR cetuximab (400/250 mg/m^2) could be considered for the patients in which bolus cisplatin (100 mg/m^2) would be contraindicated or poorly tolerated[13].
- Induction chemotherapy (i.e., TPF) is an option for individuals who have not received previous radiation therapy and who otherwise would require total laryngectomy, however based on the results of the RTOG 91-11 demonstrating improved laryngeal preservation rates with concurrent administration, induction therapy is not favoured[18].

Recommendations: Recurrent Laryngeal Cancer

Patients with recurrent disease after definitive management require discussion at multidisciplinary tumour board rounds.

Select early glottic cancer patients treated initially with surgery, may be amenable to further surgery when local recurrence occurs.

Patients initially treated with definitive radiation may be amenable to surgical salvage.

Surgical salvage may involve partial laryngectomy (in select patients) or total laryngectomy.

Radiotherapy:[3] ***(Level of Evidence II Strength of Recommendation B)***

- If no prior RT, the recommended RT dose after surgery for recurrent laryngeal cancer is 60 - 66 Gy (2.0Gy/fraction – 2.2 Gy/fraction).

Systemic Therapy Combined with Radiotherapy for Curative-Intent HNSCC:

Standard chemotherapy regimens for locally advanced and locally recurrent disease include:

- Cisplatin (100 mg/m^2) on days 1, 21, 43 when combined with radiation.
- Alternative Cisplatin delivery schedule daily (6mg/m2), weekly (40mg/m^2) OR Cetuximab (400/250 mg/m^2) could be considered for the patients in which bolus Cisplatin (100 mg/m^2) would be contraindicated or poorly tolerated[13].
- Induction chemotherapy (i.e., TPF) is an option for individuals who have not received previous radiation therapy and who otherwise would require total laryngectomy, however based on the results of the RTOG 91-11 demonstrating improved laryngeal preservation rates with concurrent administration, induction therapy is not favoured[18].

Palliative Treatment Recommendations: ***(Level of Evidence I Strength of Recommendation A)***[8]

- Pembrolizumab, either as monotherapy (must be PD-L1 positive by CPS) or in combination with platinum doublet (any PD-L1 status) is recommended for patients with recurrent/metastatic laryngeal cancer.
- If not previously exposed to a checkpoint inhibitor in the first line setting, nivolumab is recommended in the second line setting.
- Patients with poor performance status and cancers not amenable to curative-intent strategies are managed with best supportive care.

Speech Language Pathology in Management Of Laryngeal Cancer

(Level of Evidence III Strength of Recommendation B)

Speech language pathologists (SLP) have important roles in the early and long-term management of patients with laryngeal cancer, relating to speech and swallowing changes associated with adaptations to impairments from disease and treatment

Early Glottic Cancer

- Pre- and post-treatment SLP assessment is not mandatory for all early glottic patients, but can be considered
- Patients undergoing primary radiation or partial laryngectomy would benefit from baseline assessment, follow-up, and treatment for treatment-related voice and swallowing issues

Advanced Glottic Cancer[3, 20, 21]

- Pre- and post-treatment SLP assessment is recommended for patients treated with organ preservation
- Pre- and post-operative SLP assessment is recommended for all total laryngectomy patients
- Total laryngectomy patients need regular access to skilled SLP services for routine and urgent TEP care.
- SLP provides voice rehabilitation services including alaryngeal speech, electrolarynx, or augmentative communication devices.
- Long-term voice and swallowing assessment and rehabilitation should be offered for advanced cancer patients treated with organ preservation to address communication needs and treatment-related late effects.

Competencies for Speech Language Pathologists

- Full registration status as a Registered Speech-Language Pathologist through National Organization.
- Minimum 2-year advanced practice training prior to working with head and neck cancer patients. (Guideline HN-001)
- SLP's working with Total Laryngectomy patients, specifically Tracheoesophageal Puncture and Prosthesis should meet additional competencies. (See Appendix C)

Discussion

Initial Work-Up and Supportive Care Evaluation

Laryngeal cancer commonly presents as persistent voice change, which will often prompt an individual to see their physician. Other potential presenting symptoms include neck pain, shortness of breath, difficulty swallowing, coughing out blood, or a neck lump. A complete head and neck examination is required to begin to diagnose laryngeal cancer. For individuals with suspected laryngeal cancer, a more thorough examination including endoscopic examination of the larynx and vocal cords by a specialist is needed. The diagnosis of laryngeal cancer requires a tissue biopsy, which is critical in establishing a diagnosis and distinguishing between malignant, pre-malignant, or non-cancerous lesions that affect the larynx. Determining optimal treatment also depends on thorough evaluation of the affected portions of the larynx and surrounding areas.

Imaging studies using CT with contrast of the head and neck areas should be considered to evaluate the local and regional extent of disease. Consideration should be given to assess for metastatic disease (i.e. CT of the chest, bone scan, PET/CT etc.) based on extent of presenting disease and clinical/biochemical concerns.

As a result of the larynx's roles in speech and swallowing, Speech Language Pathology plays a fundamental role in the care of laryngeal cancer patients during and after treatment, as clinically indicated. Dental evaluation is required in all patients who require radiation treatment, prior to the commencement of treatment to assess, restore or extract decayed teeth. Finally, nutritional counselling is also valuable to optimize quality of life during and after treatment.

Treatment for Patients with Laryngeal Cancer

Owing to the anatomic and physiologic differences between the different subsites of the larynx, laryngeal cancer staging, and treatments are distinguished based on whether the primary site is located in the supraglottic, glottic, or subglottic larynx. In general, early stage cancers can be treated by single modality treatments, either surgery or radiotherapy, while later stage cancers often require a combination of surgery, radiation, and chemotherapy.

Treatment for Patients with Early-Stage Laryngeal Cancer (T1-T2, N0, M0)

For patients with early stage laryngeal cancers, equivalent outcomes can be expected employing either surgery or RT alone but require patient selection to determine the optimal treatment modality. Guidelines published by the European Society for Clinical Oncology[4], National Comprehensive Cancer Network[3], and ASCO[2] support this recommendation. Evidence suggests that the overall survival (OS) rate for patients with early stage laryngeal cancer is approximately 60% to 90% with either surgery or radiotherapy, but large variability exists between the different subsites. Glottic cancers tend to present with smaller, less advanced disease since change in voice is a common early symptom and subsequently have the highest survival rates.

The consensus from the Alberta Provincial Head and Neck Tumour Team is that radiation doses of 63 Gy (2.25 Gy/fraction) to 66 Gy (2.0 Gy/fraction) over 6 to 7 weeks (daily, Monday to Friday) is needed for primary tumour treatment for T1 glottic cancers. Glottic T2 cancers, supraglottic, and subglottic cancers are treated with higher doses 65.25 Gy (2.25 Gy/fraction) to 70 Gy (2.0 Gy/fraction). Elective treatment of the neck is not recommended for glottic cancers but is recommended for supraglottic cancers.

Treatment for Patients with Advanced-Stage Laryngeal Cancer (T3-T4; N1–3; T2–4 , Any N)

While single modality treatment has good success in Stage I and Stage II laryngeal cancers, more intensive treatment strategies are recommended to manage advanced-stage disease. Organ preservation strategies are effective for T3 disease (tumours confined to the larynx). Five-year overall survival rates are similar between patients treated by surgery plus adjuvant radiotherapy compared to patients receiving chemoradiotherapy, once adjustment for patients with severe comorbidities are taken into account since a larger portion of patients with severe comorbidities are treated by organ preservation therapy than surgery[22]. The addition of chemotherapy to radiotherapy improves locoregional control and larynx preservation rates in organ preservation protocols compared to RT alone [23].

In patients with T4a tumours, better overall survival is reached with total laryngectomy, particularly among patients with lower nodal burden of disease [24, 25]. The effect on survival rates caused by aspiration pneumonia in patients with a non-functional larynx among patients treated with organ preservation versus total laryngectomy is inadequately defined. Overall survival rates decrease at a greater rate than disease free survival and locoregional control rates between 5 – 10 years post-treatment, indicating additional factors beyond laryngeal oncologic disease impact this population [26].

Treatment for Patients with Distant Metastatic Disease (Any T, Any N, M1)

Patients with laryngeal cancer present with distant metastasis in approximately 3% of cases[27]. Treatment is often palliative in nature and should be directed to minimize symptoms and maintain maximum quality of life. RT can be administered to palliate symptoms. Participation in a clinical trial, if available, is the preferred treatment option. Referral to palliative care programs should be considered early in the patient's care to help relieve suffering and improve quality of life. Speech-Language Pathologists should participate in the palliation of dysphagia. Clinical and instrumental assessment can be provided as necessary. Management of aspiration should take into account the patient's wishes and informed choice, as well as their tolerance of aspiration.

Treatment for Patients with Recurrent or Persistent Disease

Patients with recurrent or persistent laryngeal cancer should be restaged after primary treatment to assess local, regional and distant disease. Approximately 4% of patients with glottic cancer, 16% with supraglottic, and 11% with subglottic squamous cell cancers will develop delayed regional metastasis[28]. PET can detect head and neck tumour recurrence when it may be undetectable by other clinical methods [29]. As clinically indicated a confirmatory mucosal biopsy of the area in question or needle biopsy of a concerning lymph node/deep tissue is recommended. Treatment should be individualized based on patient performance status and extent of disease. Laser excision of small recurrences can be considered however for more extensive disease total laryngectomy may be required, particularly in the previously irradiated patient. Chemotherapy can also be utilized as appropriate.

References

1. Jones TM, De M, Foran B, Harrington K, et al. Laryngeal cancer: United Kingdom National Multidisciplinary guidelines. *J Laryngol Otol*. May 2016;130(S2):S75-S82.

2. Pfister DG, Laurie SA, Weinstein GS, et al. American Society of Clinical Oncology clinical practice guideline for the use of larynx-preservation strategies in the treatment of laryngeal cancer. *J Clin Oncol*. Aug 01 2006;24(22):3693-704.

3. NCCN Clinical Practice Guideline in Oncology- Head and Neck Cancer- Version 3. April 27, 2021.

4. Machiels JP, René Leemans C, et al. Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 11 2020;31(11):1462-1475.

5. Voora RS, Panuganti B, Flagg M, et al. Salvage Following Transoral Laser Microsurgery for Early Glottic Cancer in National Veteran Database. *Laryngoscope*. 12 2021;131(12):2766-2772.

6. Beswick DM, Damrose EJ. Primary tracheoesophageal puncture and cricopharyngeal myotomy in stapler-assisted total laryngectomy. *J Laryngol Otol*. Jul 2016;130(7):686-90.

7. Helliwell T, J W. Dataset for histopathology reporting of mucosal malignancies of the larynx. The Royal College of Pathologists; 2013.

8. Marth C, Landoni F, Mahner S, et al. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. Jul 2017;28(suppl_4):iv72-iv83.

9. Ahn SH, Hong HJ, Kwon SY, et al. Guidelines for the Surgical Management of Laryngeal Cancer: Korean Society of Thyroid-Head and Neck Surgery. *Clin Exp Otorhinolaryngol*. Mar 2017;10(1):1-43.

10. Van Loon Y, Hendriksma M, Langeveld TPM, et al. Treatment Preferences in Patients With Early Glottic Cancer. *Ann Otol Rhinol Laryngol*. Mar 2018;127(3):139-145.

11. Silver CE, Beitler JJ, Shaha AR, et al. Current trends in initial management of laryngeal cancer: the declining use of open surgery. *Eur Arch Otorhinolaryngol*. Sep 2009;266(9):1333-52.
12. Forastiere AA, Ismaila N, Lewin JS, , et al. Use of Larynx-Preservation Strategies in the Treatment of Laryngeal Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 04 10 2018;36(11):1143-1169.

13. Ang KK, Zhang Q, Rosenthal DI, et al. Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV head and neck carcinoma: RTOG 0522. *J Clin Oncol*. Sep 20 2014;32(27):2940-50.

14. Canis M, Ihler F, Martin A, et al. Results of 226 patients with T3 laryngeal carcinoma after treatment with transoral laser microsurgery. *Head Neck*. May 2014;36(5):652-9.

15. Deganello A, Meccariello G, Bini B, et al. Is elective neck dissection necessary in cases of laryngeal recurrence after previous radiotherapy for early glottic cancer? *J Laryngol Otol*. Dec 2014;128(12):1089-94.

16. Deganello A, Gitti G, Meccariello G, et al. Effectiveness and pitfalls of elective neck dissection in N0 laryngeal cancer. *Acta Otorhinolaryngol Ital*. Aug 2011;31(4):216-21.

17. Skóra T, Nowak-Sadzikowska J, Mucha-Małecka A, et al . Postoperative irradiation in patients with pT3-4N0 laryngeal cancer: results and prognostic factors. *Eur Arch Otorhinolaryngol*. Mar 2015;272(3):673-9.

18. Cooper JS, Zhang Q, Pajak TF, et al. Long-term follow-up of the RTOG 9501/intergroup phase III trial: postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys*. Dec 01 2012;84(5):1198-205.

19. Hans S, Chekkoury-Idrissi Y, Circiu MP, et al. Surgical, Oncological, and Functional Outcomes of Transoral Robotic Supraglottic Laryngectomy. *Laryngoscope*. 05 2021;131(5):1060-1065.

20. *Speech-Language Pathology Medical Review Guidelines: Laryngeal Cancer*. American Speech-Language-Hearing Association (ASHA); 2015.

21. Clinical Practice Guideline: Communication Health Assistant: Verifying Education, Training and Competence. College of Speech and hearing Health Professionals of British Columbia; 2021.

22. Connor KL, Pattle S, Kerr GR,et al. Treatment, comorbidity and survival in stage III laryngeal cancer. *Head Neck*. May 2015;37(5):698-706.

23. Forastiere AA, Zhang Q, Weber RS, et al. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. *J Clin Oncol*. Mar 01 2013;31(7):845-52.

24. Francis E, Matar N, Khoueir N, et al. T4a laryngeal cancer survival: retrospective institutional analysis and systematic review. *Laryngoscope*. Jul 2014;124(7):1618-23.
25. Choi YS, Park SG, Song EK, et al. Comparison of the therapeutic effects of total laryngectomy and a larynx-preservation approach in patients with T4a laryngeal cancer and thyroid cartilage invasion: A multicenter retrospective review. *Head Neck*. 08 2016;38(8):1271-7.

26. Rosenthal DI, Mohamed AS, Weber RS, et al. Long-term outcomes after surgical or nonsurgical initial therapy for patients with T4 squamous cell carcinoma of the larynx: A 3-decade survey. *Cancer*. May 15 2015;121(10):1608-19.

27. Pan Y, Hong Y, Liang Z, et al. Survival analysis of distant metastasis of laryngeal carcinoma: analysis based on SEER database. *Eur Arch Otorhinolaryngol*. Jan 2019;276(1):193-201.

28. Spector JG, Sessions DG, Haughey BH, et al. Delayed regional metastases, distant metastases, and second primary malignancies in squamous cell carcinomas of the larynx and hypopharynx. *Laryngoscope*. Jun 2001;111(6):1079-87.

29. Lowe VJ, Boyd JH, Dunphy FR, et al. Surveillance for recurrent head and neck cancer using positron emission tomography. *J Clin Oncol*. Feb 2000;18(3):651-8.

30. Protocol for the Examination of Specimens From Patients With Cancer of the Larynx. https://documentscaporg/protocols/cp-headandneck-larynx-17protocol-4001pdf: Collage of American Pathologists; June: 2017.

31. Lewis JS, Beadle B, Bishop JA, et al. Human Papillomavirus Testing in Head and Neck Carcinomas: Guideline From the College of American Pathologists. *Arch Pathol Lab Med*. May 2018;142(5):559-597.

32. Clarke P, Radford K, Coffey M, et al. Speech and swallow rehabilitation in head and neck cancer: United Kingdom National Multidisciplinary Guidelines. *J Laryngol Otol*. May 2016;130(S2):S176-S180.

33. Brook I, Goodman JF. Tracheoesophageal Voice Prosthesis Use and Maintenance in Laryngectomees. *Int Arch Otorhinolaryngol*. Oct 2020;24(4):e535-e538.

Appendix A: TNM Staging of Laryngeal Cancers

Table 1. TNM Classification AJCC 8th Ed.

Glottic laryngeal cancer **Primary tumour (T)**	
Tis	Tumour is only in the top layer of cells lining the inside of the larynx and has not grown any deeper.
T1a	The tumor is only in the right or left vocal cord
T1b	The tumor is in both vocal folds
T2	Tumour has grown into the supraglottis or subglottis, and/or the vocal cords do not move normally
T3	Tumour is still only in the larynx, but it has caused a vocal cord to stop moving, OR the tumour is growing into the paraglottic space, OR the tumour is growing into the inner part of the thyroid cartilage
T4a	The tumor has grown through the thyroid cartilage and/or is growing into tissues beyond the larynx
T4b	Tumour is growing into the area in front of the spine in the neck, surrounds a carotid artery, or is growing down into the space between the lungs
Regional lymph nodes (N)	
N0	The cancer has not spread to nearby lymph nodes
N1	The cancer has spread to a single lymph node on the same side of the neck as the tumour, which is no larger than 3 cm across
N2	The Cancer has spread to a single or more than one lymph node which is larger than 3 cm but no larger than 6 cm across,
N3	The cancer has spread to at least one lymph node that is larger than 6 cm across, or it has spread to a lymph node and then grown outside of the lymph node
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
Supraglottic laryngeal cancer **Primary tumour (T)**	
Tis	Tumour is only in the top layer of cells lining the inside of the larynx and has not grown any deeper.
T1	Tumour has grown deeper, but it is only in the supraglottis
T2	Tumour has grown deeper and/or the vocal cords move normally
T3	Tumour is still only in the larynx, but it has caused a vocal cord to stop moving, OR the tumour is growing into the paraglottic space, OR the tumour is growing into the inner part of the thyroid cartilage
T4a	Tumour might or have grown into thyroid cartilage and/or is growing into tissues beyond the larynx
T4b	Tumour is growing into the area in front of the spine in the neck, surrounds a carotid artery, or is growing down into the space between the lungs
Regional lymph nodes (N)	
N0	The cancer has not spread to nearby lymph nodes
N1	The cancer has spread to a single lymph node on the same side of the neck as the tumour, which is no larger than 3 cm across
N2	The Cancer has spread to a single or more than one lymph node which is larger than 3 cm but no larger than 6 cm across,
N3	The cancer has spread to at least one lymph node that is larger than 6 cm across, or it has spread to a lymph node and then grown outside of the lymph node
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Appendix B: Pathologic Evaluation and Reporting of Laryngeal Specimens

Submission of Laryngeal Representative Biopsies and Cord Excisional Biopsies:

- Submission of laryngeal biopsies require some experience by a surgeon for handling, processing, and labeling of specimens.
- Biopsy specimens must be clearly labelled as to the specimen type (representative biopsy versus excisional) and include clinical history, including if suspicious for invasive disease.
- Superficial biopsies may not be adequately representative for assessment of invasion.
- If a specimen submitted is meant to be excisional, this must be clearly stated on the requisition with orientation provided.
- Special techniques exist for specimen orientation and should be employed by the surgeon to optimize handling by the laboratory.

Pathologic Reporting of Laryngeal Biopsies and Cord Excisions[7]:

- For laryngeal carcinomas, a biopsy should report at minimum: presence or absence of invasion and histologic type as per WHO classification.
- For pre-invasive lesions, different grading systems exist which show poor reproducibility between pathologists.
- The WHO uses a 2-tier system but 3-tier systems also exist. Regardless of the system used, the distinction of carcinoma in-situ is recommended.
- If sufficient subepithelial stroma is not present to assess for invasion, this should be clearly stated by the pathologist.
- Given the complex nature of these specimens, prospective review of all "Laryngeal biopsies of keratinizing lesions or lesions suspected to be dysplastic or malignant" by a subspecialty Head & Neck pathologist is recommended as per Alberta Precision Laboratories policy). This can be requested by the physician if not yet done.

***Synoptic Reporting of Laryngectomy Specimens[30]*:**

- Synoptic reporting is required for all laryngectomy specimens with carcinoma and melanoma. This is done with CAP synoptic reports which captures the ICCR Data Set for Larynx and AJCC Staging systems and includes all relevant prognostic elements.
- WHO histologic type and grading is reported.
- Margins reported with distance in mm. If tumor bed margins are used, these should be separately reported from the main specimen.

***HPV Testing*: [7, 31]**

- p16/HPV testing of laryngeal cancers should NOT routinely be performed.
- In certain circumstances it may be appropriate and can be ordered in discussion with the pathologist.

Appendix C: Role of Speech Language Pathology in Management of Laryngeal Cancer

Speech language pathologists have important roles in the early and long-term management of laryngeal cancers, with valuable guidance and care related to voice rehabilitation, swallow therapy, and TEP maintenance. Patients who undergo advanced laryngeal cancer treatments generally require more intensive involvement and therapy than the early laryngeal cancer population.

Early Glottic Cancer

Treatment:[2, 3, 21]

While pre- and post-treatment SLP assessment are not mandatory for all early glottic patients, a referral may be needed based on individual patient need for education, voice and swallowing assessment and therapy. Although the evidence for voice and swallowing therapy in this population is still inconclusive, specific groups of patients do benefit from such assessment and therapy. This includes patients undergoing organ preservation or open partial laryngectomy. Voice therapy may be recommended upfront based on video-stroboscopy findings or SLP assessment. Functional assessment of swallowing and swallowing rehabilitation may be necessary for patients after transoral surgery or open partial laryngectomy.

Follow up and Rehabilitation[3, 32]
Voice assessment and voice therapy is optional for early glottic cancer patients, however patients with ongoing abnormal function should be referred to and have ongoing access to SLP. Similarly, patients reporting difficulty with deglutition can be considered for swallowing investigations.

Advanced Glottic Cancer[3, 21]

Treatment:

Pre- and post-operative SLP assessment is recommended for all total laryngectomy patients with a focus on education about changes in anatomy, voice production, swallowing and breathing function in the preoperative setting. This will also include functional compensation, anticipated need for specialized equipment, available funding options, stoma and tracheoesophageal prosthesis care including emergencies, and follow-up process[9].

Post-operative total laryngectomy patients need access to SLP services for routine and urgent TEP care, maintenance, and stoma care. This may or may not require involvement of an otolaryngology-head and neck surgeon. SLP will initiate voice restoration when appropriate, including insertion of tracheoesophageal prosthesis (TEP), use of electrolarynx, or augmentative communication devices. Patients who elect for alaryngeal voice will receive education and training in these techniques. Speech and swallowing will be assessed and treated as needed, with voice assessment and voice therapy recommended for advanced cancer patients[33].

Follow-up and Rehabilitation[3]:

Voice and swallowing assessment and rehabilitation should be offered for advanced laryngeal cancer patients treated with organ preservation to address communication needs and treatment-related late effects. Patients treated with total laryngectomy will require ongoing follow-up and functional assessment as needed to address unique alaryngeal speech and swallowing needs. Patients with ongoing abnormal function should be seen regularly by SLP and continued at least until the patient has achieved a stable baseline following treatment. Patients with ongoing chronic speech and swallowing challenges may require indefinite follow-up by SLP.

Competencies for Speech Language Pathologists

- SLP's working with Total Laryngectomy patients, specifically Tracheoesophageal Puncture and Prosthesis should meet additional competencies.
    - National certification is necessary to qualify a person to perform preferred practice patterns in speech –language pathology for tracheoesophageal puncture and prosthesis.
    - Working alongside an experienced mentor in a training setting that allows for hands on practical experience with this population for 6 months –1 year depending on number of patients seen
    - Lengthy and Specific list of Knowledge and Skills related to this population, including a minimum number of prosthesis insertions.

Development and Revision History

This guideline was reviewed and endorsed by the Alberta Provincial Head and Neck Tumour Team. Members include otolaryngology – head and neck surgeons, radiation oncologists, medical oncologists, dentists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Head and Neck Tumour Team, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in 2022.

Levels of Evidence

I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinion

Strength of Recommendations

A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended

Maintenance

A formal review of the guideline will be conducted in 2025. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

cN0, clinically negative neck; CT, computed tomography; OS , Overall Survival; PET, positron emission tomography; SLP, Speech Language Pathology; TEP, Tracheo-Esophageal-Puncture; TLM, transoral laser microsurgery; TNM, tumour node metastasis;

Disclaimer

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.

Funding Source

Financial support for the development of Cancer Care Alberta's evidence-based clinical practice guidelines and supporting materials comes from the Cancer Care Alberta operating budget; no outside commercial funding was received to support the development of this document.

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*.

Conflict of Interest Statements

Dr. Erin Chapman has nothing to disclose
Dr. Shamir Chandarana has nothing to disclose
Dr. Dan O'Connell has nothing to disclose
Dr. Martin Hyrcza has nothing to disclose
Dr. Caroline Jeffery* has nothing to disclose
Dr. Wayne Matthews has nothing to disclose
Ms. Alanna Mcdonough has nothing to disclose
Dr. Harvey Quan has nothing to disclose
Dr. Derrick Randall* has nothing to disclose
Dr. Rufus Scrimger has nothing to disclose
Ms. Ritu Sharma has nothing to disclose
Ms. Anna Sytsanko has nothing to disclose
Dr. Marc Webster has nothing to disclose

*** Guideline working group leads**