Early & Late Laryngeal Cancer (ECPG)

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1Otorhinolaryngology Department, Faculty of Medicine/ Cairo University, 2Otorhinolaryngology Department, Faculty of Medicine/ Menoufia University, 3Otorhinolaryngology Department, Faculty of Medicine/Minia University, 4Otorhinolaryngology Department, Faculty of Medicine/ Beni-Suef University, 5Otorhinolaryngology Department, Faculty of Medicine/ Mansoura University, 6Otorhinolaryngology, H&N Department, Faculty of Medicine/Tanta

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Abbreviations

CIS	Carcinoma in situ
RT	Radiotherapy
VPL	Vertical partial laryngectomy
CPG	Clinical Practice Guideline
GRADE	Grading of Recommendations Assessment, Development and Evaluation
NCCN	National Comprehensive Cancer Network
MRI	Magnetic Resonance Imaging

Executive Summary

The purpose of this guideline is to identify quality improvement opportunities in the assessment, diagnosis, and management of laryngeal cancer and to create explicit and actionable recommendations to implement these opportunities in clinical practice.

1. *Definition and incidence: The larynx is divided into 3 regions: supraglottis, glottis, and subglottis. The distribution of cancers is as follows: 30% to 35% in the supraglottic region, 60% to 65% in the glottic region, and 5% in the subglottic region. The incidence and pattern of metastatic spread to regional nodes vary with the primary region.* ***(Strong Recommendation)***
2. *Multidisciplinary consultation is critical for laryngeal cancer management because of the potential for loss of speech and, in some instances, for swallowing dysfunction. (Referral to tertiary care center with radiotherapy and partial laryngectomy facilities and multidisciplinary medical teams available is recommended)* ***(Strong Recommendation)***
3. *For patients with carcinoma in situ of the larynx, recommended treatment options include: 1) endoscopic removal (ie, stripping, laser), which is preferred; or 2) RT. (Meticulous follow-up is then mandatory).* ***(Strong Recommendation)***
4. *A. For early stage glottic or supraglottic cancer, surgery or RT have similar effectiveness, the choice of treatment modality depends on anticipated functional outcome, the patient's wishes, reliability of follow-up, and general medical condition (Open partial laryngectomy as VPL and supraglottic laryngectomy, are valid options in selected cases).* ***(Strong Recommendation)***

B. Adjuvant treatment depends on the presence (or absence) of adverse features. Adjuvant treatment for selected patients with T1-2, and N0 supraglottic cancer may include re-resection if there are positive margins. For selected patients with T1-3, N+ supraglottic disease, re-resection may be attempted if negative margins are feasible and can be achieved without total laryngectomy, and if re-resection has the potential to change the indication for adjuvant systemic therapy/RT. ***(Strong Recommendation)***

5. *A. Resectable, advanced stage glottic and supraglottic primaries are usually managed with a combined modality approach. If treated with primary surgery, total laryngectomy is usually indicated, although selected cases can be managed with conservation surgical techniques that preserve vocal function as supracricoid laryngectomy.*

Pulmonary function tests should be considered. ***(Strong Recommendation)***

B. If total laryngectomy is indicated but laryngeal preservation is desired, concurrent systemic therapy/RT is recommended. When using systemic therapy/RT, high-dose cisplatin is preferred (at 100 mg/m2 on days 1, 22, and 43). Induction chemotherapy with management based on response is an option for all but T1-2, and N0 glottic cancer. ***(Strong Recommendation)***

C. Definitive RT (without systemic therapy) is an option for patients with T3, and N0-1 disease who are medically unfit or refuse systemic therapy. Surgery is reserved for managing the neck as indicated, for those patients whose disease persists after systemic therapy/RT or RT, or for those patients who develop a subsequent locoregional recurrence. ***(Strong Recommendation)***

D.Management of locally advanced, resectable glottic and supraglottic cancers (in which total laryngectomy is indicated but laryngeal preservation is desired) with concurrent cisplatin and radiation. Concurrent RT and systemic therapy (eg, cisplatin 100 mg/m2 preferred) is the recommended option for achieving laryngeal preservation with Long-term follow-up (10 years). ***(Strong Recommendation)***

E. In cases with T3 laryngeal cancer if IMRT and modern radiotherapy are available and affordable, concomitant radiotherapy with systemic therapy in the form of cisplastin can be tried as an organ preservation treatment. ***(Strong Recommendation)***

F. For patients with glottic and supraglottic T4a tumors, the recommended treatment approach is total laryngectomy with thyroidectomy and neck dissection as indicated (depending on node involvement) followed by adjuvant treatment (RT, or systemic therapy/RT may be considered).

G. For patients with glottic T4a laryngeal cancer, postoperative observation is an option for highly selected patients with good-risk features (eg, indolent histopathology). For selected patients with T4a tumors who decline surgery, the NCCN Panel recommends: 1) considering concurrent chemoradiation; 2) clinical trials; or 3) induction chemotherapy with additional management based on response. ***(Strong Recommendation)***

6. *Follow-up examinations in patients treated from laryngeal caner may need to be supplemented with serial endoscopy or high-resolution, advanced radiologic imaging techniques because of the scarring.* ***(Strong Recommendation)***

Introduction, scope and audience

Introduction and definitions

Laryngeal carcinoma is the most common site of malignancy in the head and neck worldwide. The effects of the disease process and the treatment can have a significant impact on voice and swallow function and quality of life. Recent advances i.e., surgical, and non-surgical management options are available.

***Scope**:*

The purpose of this guideline is to identify quality improvement opportunities in the assessment, diagnosis, and management of laryngeal cancer and to create explicit and actionable recommendations to implement these opportunities in clinical practice. Specifically, the goals are to improve diagnostic accuracy for laryngeal cancer, promote and guide management, and the more judicious use of the surgical and non-surgical management options available.

***Target audience**:*

Target users are ENT clinicians and specialists and residents to be used for management of adult patients with cancer larynx.

Methods

Methods of development

Stakeholder Involvement: Individuals who were involved in the development process. Included the above-mentioned Head and Neck Chief Manager, Head and Neck Executive Manager, Assembly Board, Grading Board and Reviewing Board.

Information about target population experiences was not applicable for this topic.

Search Method
Pubmed, Medline, Egyptian Knowledge Bank, Medscape, WebMD, Google Scholar

Keywords
Laryngeal cancer, chemotherapy, chemoradiation, laryngeal preservation.

The adaptation cycle passed over: *set-up phase, adaptation phase (Search and screen, assessment: currency, content, quality & /decision/selection) and finalization phase that included revision and external reviewing and Other related specialties Reviewing Board including phoniatrics & speech specialist, Clinical oncology & radiotherapy specialist and nurse.*

Time period searched: *from January 2009 to March 2020***.**

Results

Three guidelines were assessed by 7 experts Laryngologists and the International Consensus on laryngeal cancer 2021 had the highest scores as regards to the currency, contents and quality. It was graded GRADE by 19 expert Laryngologists and reviewed by 3 expert reviewers. To improve quality, gather feedback on draft recommendations. The external review was done through a rating scale as well as open-ended questions. (Annexes tables 1-3) ***(1)***.

Setting: *Primary, secondary and tertiary care centers & hospitals, and related specialties.*

Interpretation of strong and conditional recommendations for an intervention [10]

Audience	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action; only a small proportion would not.	Most individuals in this situation would want the suggested course of action, but many would not

	Formal decision aides are not likely to be needed to help individuals make decisions consistent with their values and preferences.	
Clinicians	Most individuals should receive the intervention. Adherence to the recommendation could be used as a quality criterion or performance indicator.	Different choices will be appropriate for individual patients, who will require assistance in arriving at a management decision consistent with his or her values and preferences. Decision aides may be useful in helping individuals make decisions consistent with their values and preferences.
Policymakers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to Decision frameworks (GRADE Working Group 2013)

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Recommendations,

The following statements and flowchart were adapted from the National Comprehensive Cancer Network (NCCN) 2018 ***(2)****, which had the highest scores as regards the currency, contents, and quality.*

Accepted statements	
Modified statements	
Added statements	

Clinical questions	Action recommendation	Evidence Quality	Strength of Recommendation	Study Type	Reference
1-Definition and incidence	**The larynx is divided into 3 regions: supraglottis, glottis, and subglottis. The distribution of cancers is as follows: 30% to 35% in the supraglottic region, 60% to 65% in the glottic region, and 5% in the subglottic region. The incidence and pattern of metastatic spread to regional nodes vary with the primary region.**	**High**	**Strong Recommendation**	**Systematic reviews**	**(2)**
2-Nodal metastasis	**More than 50% of patients with supraglottic primaries present with spread to regional nodes because of an abundant lymphatic network that crosses the midline. Bilateral adenopathy is not uncommon with early-stage supraglottic primaries. Thus, supraglottic cancer is often locally advanced at diagnosis. In contrast, the lymphatic drainage of the glottis is sparse and early-stage primaries rarely spread to regional nodes. Because hoarseness is an early symptom, most glottic cancer is in the early stage at diagnosis. Thus, glottic cancer has an excellent cure rate of 80% to 90%. Nodal involvement adversely affects survival rates.**	**High**	**Strong Recommendation**	**Systematic reviews**	**(2, 3)**

Multidisciplinary consultation	**Multidisciplinary consultation is critical for laryngeal cancer management because of the potential for loss of speech and, in some instances, for swallowing dysfunction.**	**High**	**Strong Recommendation**	**Systematic reviews**	
4-CIS	**For patients with carcinoma in situ of the larynx, recommended treatment options include: 1) endoscopic removal (ie, stripping, laser), which is preferred; or 2) RT.** **Meticulous follow-up is then mandatory**	**High**	**Strong Recommendation**	**Systematic reviews**	**(4-7)**
5-Early laryngeal cancer	**a. For early stage glottic or supraglottic cancer, surgery or RT have similar effectiveness, the choice of treatment modality depends on the anticipated functional outcome, the patient's wishes, reliability of follow-up, and general medical condition.** **Open partial laryngectomy as VPL and supraglottic laryngectomy, are valid options in selected cases**	**High**	**Strong Recommendation**	**Systematic reviews and clinical trials**	**(6, 8)**
	b. **Adjuvant treatment depends on the presence (or absence) of adverse features. Adjuvant treatment for selected patients with T1-2, and N0 supraglottic cancer may include re-resection if there are positive margins. For selected patients with T1-3, N+ supraglottic disease, re-resection may be attempted if negative margins are feasible and can be achieved without total laryngectomy, and if re-resection has the potential to change the indication for adjuvant systemic therapy/RT.**	**High**	**Strong Recommendation**	**Clinical trials**	**(8)**
6-Late laryngeal cancer	**a. Resectable, advanced-stage glottic, and supraglottic primaries are usually managed with a combined modality approach. If treated with primary surgery, total laryngectomy is usually indicated, although selected cases can be managed with conservation surgical techniques that preserve vocal function as supra cricoid laryngectomy. Pulmonary**	**High**	**Strong Recommendation**	**Clinical trials**	**(9)**

	function tests should be considered before surgery.				
	b. If total laryngectomy is indicated but laryngeal preservation is desired, concurrent systemic therapy/RT is recommended. When using systemic therapy/RT, high-dose cisplatin is preferred (at 100 mg/m2 on days 1, 22, and 43). Induction chemotherapy with management based on response is an option for all but T1-2, and N0 glottic cancer.	**High**	**Strong Recommendation**	**Clinical trials**	**(10)**
	c. Definitive RT (without systemic therapy) is an option for patients with T3, and N0-1 disease who are medically unfit or refuse systemic therapy. Surgery is reserved for managing the neck as indicated, for those patients whose disease persists after systemic therapy/RT or RT, or for those patients who develop a subsequent locoregional recurrence.	**moderate**	**Conditional recommendation**	**Clinical trials**	**(9, 10)**
	d. Management of locally advanced, resectable glottic and supraglottic cancers (in which total laryngectomy is indicated but laryngeal preservation is desired) with concurrent cisplatin and radiation. Concurrent RT and systemic therapy (eg, cisplatin 100 mg/m2 preferred) is the recommended option for achieving laryngeal preservation with Long-term follow-up (10 years).	**High**	**Strong Recommendation**	**Clinical trials**	**(9)**
	e. In cases with T3 laryngeal cancer, if IMRT and modern radiotherapy are available and affordable, concomitant radiotherapy with systemic therapy in the form of cisplatin can be tried as an organ preservation treatment.	**High**	**Strong Recommendation**	**Clinical trials**	**(9)**

	f. For patients with glottic and supraglottic T4a tumors, the recommended treatment approach is total laryngectomy with thyroidectomy and neck dissection as indicated (depending on node involvement) followed by adjuvant treatment (RT, or systemic therapy/RT may be considered).	High	Strong Recommendation	Clinical trials	(9, 10)
	g. For patients with glottic T4a laryngeal cancer, postoperative observation is an option for highly selected patients with good-risk features (eg, indolent histopathology). For selected patients with T4a tumors who decline surgery, the NCCN Panel recommends: 1) considering concurrent chemoradiation; 2) clinical trials; or 3) induction chemotherapy with additional management based on response.	moderate	Conditional recommendation	Clinical trials	(9)
7-follow up	Follow-up examinations in patients treated with laryngeal cancer may need to be supplemented with serial endoscopy or high-resolution, advanced radiologic imaging techniques because of the scarring, edema, and fibrosis that occur in the laryngeal tissues and neck after high-dose radiation.	High	Strong Recommendation	Systematic reviews	(2)

Research needs

There is a need to conduct randomized controlled trials (RCTs) to further assess several problems of involvement of the anterior commissure.
There is a need to conduct randomized controlled trials (RCTs) to further assess what is the appropriate treatment of the regional cervical nodes for patients with laryngeal cancer who are treated with an organ-preservation approach?
There is a need to conduct randomized controlled trials (RCTs) to further assess the role of elective neck dissection in patients with radio-recurrent and radio-residual laryngeal cancer?

Monitoring and evaluating the impact of the guideline

Monitoring/ Auditing Criteria:

- *Acquire full history from patients.*
- *Ensure multidisciplinary team management of cancer larynx patients.*
- *Perform laryngoscopic examination to all patients with cancer larynx.*
- *Perform direct laryngoscopic examination to all patients with cancer larynx and take biopsies for histopathological examination.*
- *Discuss with the patients with different management options.*
- *Perform regular follow up for treated patients including serial endoscopic examinations and imaging studies.*
- *All clinicians should be aware and informed to consider the following:*
- *Red Flags that need urgent referral for Assessment/ Management must be taken into consideration.*
- *For Assessment it is crucial to perform a detailed history/ clinical examination as a minimum patient assessment.*

Updating of the guideline

Updating Procedure:
Any recommendation of this guideline will be updated when new evidence that could potentially impact the current evidence base for this recommendation is identified. If no new reports or information are identified for a particular recommendation, the recommendation will be revalidated. The focus will be on recommendations supported by very-low- or low certainty evidence and where new recommendations or a change in the published recommendations may be needed.

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Further Reading

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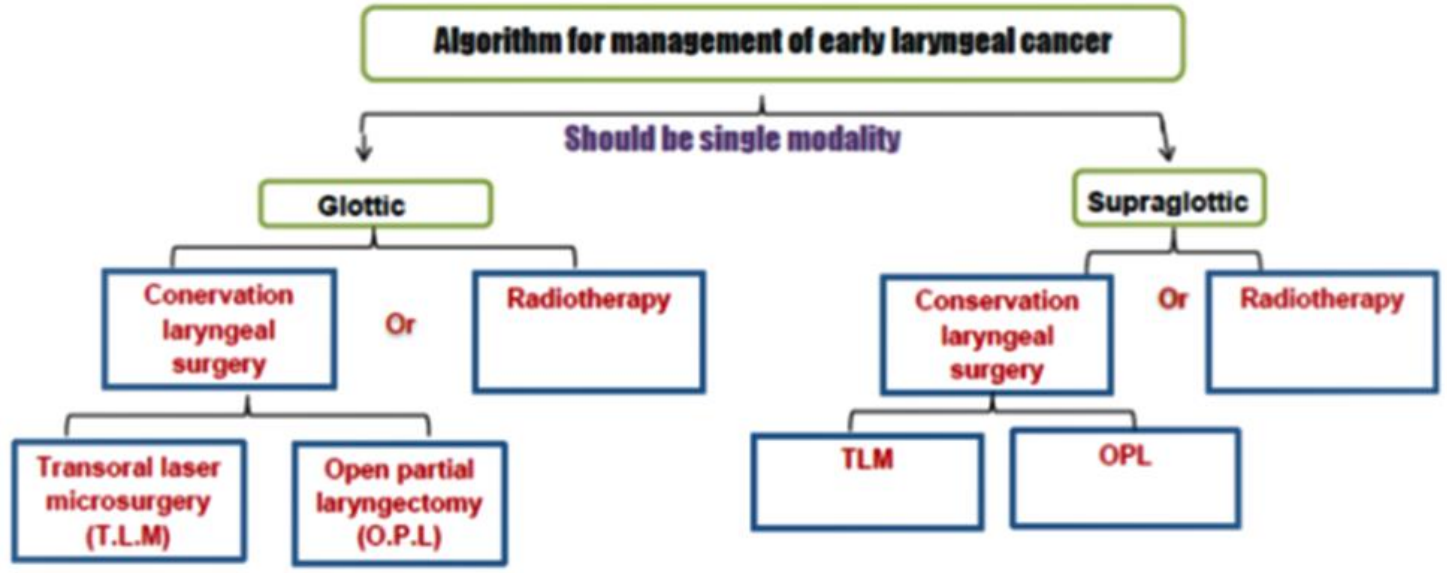
Annexes

Editorial Independence:

- *This guideline was developed without any external funding.*
- *All the guideline development group members have declared that they do not have any competing interests.*

Annex 1: <u>Guideline Flowchart</u>



- Assuming guarantee of adequate surgical exposure & surgeon experience

- Vertical hemilanying ectomy (V.L) when TLM is not feasible because of extension to adjacent site/ tumor bulk or difficult surgical exposure)
- In cases with anterior commissure extension either frontolateral vertical hemilaryngectomy or surpracricoid laryngectomy (S.C.L)

- If exposure that ensures adequate margin resection during T.L.M is questionable → O.P.L or Radiotherapy

N_0 neck

Elective neck dissection is not recommended in T_1 N0 & T_2 N_0 glottic cancer

N0 neck

- Bilateral SND (II, III, IV)

Algorithm for surgical management of advanced laryngeal cancer

Glottic

T_3

T.L.M Or O.P.L

Postoperative radiotherapy

O.P.L (hemilaryngectomy or SCL- CHEP) could be performed if:

- no arytenoid joint fixation
- no cricoid orthyroid cartilage invasion.
- no extra-laryngeal spread

T_4

Total laryngectomy + ND

If T.L.M is not feasible or OPL is contraindicated

Total laryngectomy + ND

- Patients with subglottic extension > 10 mm or transglottic extension → Ipsilateral thyroid lobectomy + Isthmusectomy

N0 neck

Ipsilateral SND (II, III, IV) (NB; recently consider superselective VI, IIA, III)

N + ve Neck

Bil. SND (II, III, IV)

Suproglottic

Total laryngectomy + ND

- O.P.L ; in selected cases;
  - No invasion of tongue base
  - No cricoarytenoid joint fixation
  - No inferior extension to cricoid cartilage

**With increased post operative comorbidity compared to total laryngectomy

N0 neck

Bil. SND (II, III, IV)

N + ve Neck

Bil. SND (II, III, IV) + post op. R.T or C.R.T

Annex 2: Tables of appraisal of selected guidelines: Currency (table 1), Content (table 2) and Quality (table 3) of the selected guidelines.

Table (1): Assessment of Currency.

No	Guideline Name	Year of publication	The organization	Age demography
1	**United Kingdom National Multidisciplinary Guidelines for Head and Neck Cancer(5th edition)**	2016	Developed by an expert team, often multidisciplinary. An affirmation of the truly multidisciplinary nature of these guidelines is the endorsement by seven medical specialty organizations involved in head and neck cancer care in the UK: British Association of Endocrine and Thyroid Surgeons, British Association of Head and Neck Oncologists, British Association of Oral and Maxillofacial Surgeons, British Association of Otorhinolaryngology-Head and Neck Surgery, British Association of Plastic, Reconstructive and Aesthetic Surgeons, The Royal College of Pathologists and The Royal College of Radiologists (Faculty of Clinical Oncology). The guidelines will be of interest across the spectrum of healthcare professionals who Look after patients with Head and Neck Cancer.	adult
2	**NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)**	2018	The NCCN Guidelines Development Group comprises the NCCN Guidelines Steering Committee, Panels specific to each of the Guidelines, and the NCCN Headquarters Team that supports the Panels and Guidelines activities. Each NCCN Guidelines Panel includes a Panel Chair, Vice-Chair (or Co-Chair), and a group of representatives from the NCCN Member Institutions. Panel membership may also include a primary care physician, a patient advocate, and, in special circumstances, additional members from the NCCN Member Institutions, for a broad representation of specialties and clinical expertise. Developed by an alliance of leading 28 cancer centers the in the USA	adult
3	**Guidelines for the Surgical Management of Laryngeal Cancer: Korean Society of Thyroid-Head and Neck Surgery**	2017	Korean Society of Thyroid-Head and Neck Surgery appointed a Task Force to develop clinical practice guidelines for the surgical treatment of laryngeal cancer.	adult

Table (2): Assessment of contents.

Domain	UK Guidelines	NCCN Guidelines	SK Guidelines
Credibility	9	9	8
Observability	7	9	3
Relevance	7	9	5
Relative advantage	8	9	6
Easy to install/understand	8	9	9
Testability	7	9	6
Compatibility	7	8	9
Total score	53	62	46

- **NCCN Guidelines had the highest scores.**

Table (3): Assessment of quality (CPG Appraisal tool).

Domain	UK Guidelines	NCCN Guidelines	SK Guidelines
1.Transparency	A	A	B
2. Conflict of interest	A	A	A
3. Development Group	A	A	B
4. Systematic review	B	A	B
5. Grading of evidence	B	A	A
6. Recommendations	B	A	B
7. External review	B	A	B
8. Updating	A	A	B

Annex 3: The risks and benefits of added and/or modified statements

Statement topic	Original statement	Benefits	Risks
4.CIS: For patients with carcinoma in situ of the larynx, recommended treatment options include: 1) endoscopic removal (ie, stripping, laser), which is preferred; or 2) RT. Meticulous follow-up is then mandatory	For patients with carcinoma in situ of the larynx, recommended treatment options include: 1) endoscopic removal (ie, stripping, laser), which is preferred; or 2) RT.	After treatment of CIS, Meticulous follow-up is then mandatory to detect any recurrence.	No risks.
5.Early laryngeal cancer: **a. For early stage glottic or supraglottic cancer, surgery or RT have similar effectiveness, the choice of treatment modality depends on the anticipated functional outcome, the patient's wishes, reliability of follow-up, and general medical condition. Open partial laryngectomy as VPL and supraglottic laryngectomy, are valid options in selected cases**	For early stage glottic or supraglottic cancer, surgery or RT have similar effectiveness, the choice of treatment modality depends on the anticipated functional outcome, the patient's wishes, reliability of follow-up, and general medical condition.	Selected cases could benefit from surgical option of partial laryngectomy. Avoids rdiotherapy adverse effects.	Locoregional recurrence and needing of adjuvant treatment.
5.Early laryngeal cancer: **b. Adjuvant treatment for early laryngeal cancer: Adjuvant treatment depends on the presence (or absence) of adverse features. Adjuvant treatment for selected patients with T1-2, and N0 supraglottic cancer may include re-resection if there are positive margins. For selected patients with T1-3, N+ supraglottic disease, re-resection may be attempted if negative margins are feasible and can be achieved without total laryngectomy, and if re-resection has the potential to change the indication for adjuvant systemic therapy/RT.**	Adjuvant treatment depends on the presence (or absence) of adverse features. Adjuvant treatment for selected patients with T1-2, and N0 supraglottic cancer may include re-resection if there are positive margins. For selected patients with T1-3, N+ supraglottic disease, re-resection may be attempted if negative margins are feasible and can be achieved without total laryngectomy, and if re-resection has the potential to change the indication for adjuvant systemic therapy/RT.consider adjuvant systmic therapy in T2N0 glottic cancer with risk features.	Avoids rdiotherapy or systemic therapy adverse effects.	No risks.

Three statements of the original guidline were modified summerized in table (4), there are no added nor omitted statements.