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Evidence-Based Series 5-2 Version 2

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

The Role of Endolaryngeal Surgery (With or Without Laser) versus Radiotherapy in the Management of Early (T1) Glottic Cancer

Members of the Head and Neck Cancer Guideline Development Group

October 16, 2023

An assessment conducted in November 2025 deferred the review of Evidence-Based Series (EBS) 5-2 Version 2. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

EBS 5-2 is comprised of 4 sections. You can access the summary and full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/521

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Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW *Search Dates*	SYSTEMATIC REVIEW *Data*	PUBLICATIONS	NOTES AND KEY CHANGES
Original version March 14, 2012	1996 to 2011	Full Report	Web publication Head Neck 2014 Curr Oncol 2013	NA
Current Version 2 October 16, 2023	2011 to 2022	New data found in Section 4: Document Assessment and Review	Updated Web publication	2012 recommendations are **ENDORSED**

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Evidence-Based Series 5-2: Section 1

The Role of Endolaryngeal Surgery (With or Without Laser) versus Radiotherapy in the Management of Early (T1) Glottic Cancer: Guideline Recommendations

QUESTION

In patients with early (T1) glottic cancer, what is the role of endolaryngeal surgery (with or without laser) versus radiation therapy, in terms of survival, locoregional control, laryngeal preservation rates and voice outcomes?

TARGET POPULATION

The target population of this guideline is adult patients with previously untreated early (T1) glottic cancers.

INTENDED USERS

This guideline is intended for use by clinicians and healthcare providers involved in the management or referral of adult patients with early (T1) glottic cancer.

RECOMMENDATION

For patients with early (T1) glottic cancer, recommended treatment options include the equally effective endolaryngeal surgery, with or without laser, or radiation therapy. The choice between treatment modalities should be based on patient and clinician preferences and general medical condition.

October 2023: It is the opinion of the Head and Neck Cancer Guideline Development Expert Panel that the following statement be added:

For patients in the T1a subgroup, treatment with surgery is preferred.

See Section 4 for details.

QUALIFYING STATEMENT

There is currently no well-designed, prospective, randomized controlled trial (RCT) that compares endolaryngeal surgery and radiation therapy. Thus, these recommendations are based primarily on other comparative study designs. Although not substantiated by the evidence, several factors are important considerations when deciding between surgery and radiotherapy for early glottic cancer. Location of disease is one factor. Anterior commissure involvement may be a factor that favours a recommendation of radiotherapy over surgery due to a common opinion that voice outcomes are particularly affected. Tumours localized to the midportion of the vocal fold, and where endoscopic accessibility is uncompromised, may be

considered ideal candidates for surgery. Other important practical considerations include the ability for patients to tolerate a general anaesthetic, which is required for surgery. In contrast, radiotherapy requires patient cooperation for daily treatment for four to six weeks. Partial laryngeal surgery, including revision endoscopic surgery, is possible for local recurrence following surgery. However, re-irradiation is not an option in cases of recurrence.

KEY EVIDENCE

There is a lack of high-quality evidence to explicitly inform the guideline question. Notwithstanding, the recommendation is based on the best available evidence and a consensus of expert clinical opinion of the Head and Neck Cancer Disease Site Group (DSG).

One meta-analysis, fifteen cohort studies and two cross-sectional studies comparing endolaryngeal surgery (with or without laser) to radiation therapy in patients with early glottic cancer comprised the evidence base.

- No statistically significant differences in overall survival or disease–free survival were detected. One retrospective cohort study (1) did report a significant (p=0.003) 15-year cause-specific survival benefit in surgically treated patients (100%) over those treated with radiation therapy (91%). This result was not consistent with four other retrospective cohort studies (2,3-5) that also considered cause-specific mortality and showed no significant differences. The meta-analysis [6] detected no statistically significant laryngectomy-free survival benefits associated with laser surgery when compared to radiation therapy (odds ratio [OR], 0.73; 95% confidence interval [CI], 0.39-1.35).
- One meta-analysis (6) found no statistically significant difference in local control between radiation therapy and laser surgery (OR, 0.66; 95% CI, 0.41 to 1.05). One (7) of eight retrospective cohort studies reported a marginally significant better control rate in surgically treated patients (89%) over those treated with radiotherapy (75%) when only T1a patients were considered (p=0.05). One retrospective cohort study [1] also reported a significant difference in recurrence rates favouring surgery. Thurnher et al (1) found a recurrence rate of 30.5% in those undergoing radiation therapy versus 9.9% in the patients treated with laser excision (p=0.001). The remaining five studies did not report any such significant differences in recurrence rates between treatment groups.
- Laryngeal preservation rates were found to be better with surgery, (with or without laser) as compared to radiation in five studies (1,5,7-9), while one study found a marginally significant better preservation rate with radiation therapy (p=0.051) (10).
- Post-treatment voice and speech quality was assessed by clinician perceptual analysis in one retrospective cohort study (11), which found that the difference between radiation therapy patients and those treated surgically did not reach statistical significance. In five studies that analyzed patient self-perception, three (12-14) found no statistically significant difference between treatment groups, one (15) found radiation therapy patients scored significantly better, and one (16) study reported surgically treated patients scored better. One meta-analysis (6) found conflicting results. It detected significantly better maximum phonation time and fundamental frequency in the radiation therapy patients but reported that the perturbation measures of jitter and shimmer significantly favoured the patients undergoing transoral laser surgery.

FUTURE RESEARCH

Carcinoma of the glottis is usually diagnosed in the early phase, and both modalities of treatment have shown high cure rates. However, controversies in the treatment of early glottic cancer remain because of the lack of high-quality prospective analyses comparing endoscopic

surgery versus radiotherapy. There is no evidence in favour of one treatment modality when considering the likelihood of local control or overall survival. There is a suggestion that radiotherapy may be associated with less measureable perturbation of voice as compared to surgery but no significant differences were seen in patient perception. The likelihood of laryngeal preservation may be higher when surgery can be offered as initial treatment. Future research should focus on conducting RCTs or prospective comparative studies, with ample follow-up time, that focus on functional outcomes of patients with early glottic cancer.

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Evidence-Based Series 5-2: Section 2

The Role of Endolaryngeal Surgery (With or Without Laser) versus Radiotherapy in the Management of Early (T1) Glottic Cancer: Evidentiary Base

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A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: March 14, 2012

QUESTION

In patients with early (T1) glottic cancer, what is the role of endolaryngeal surgery (with or without laser) versus radiation therapy, in terms of survival, locoregional control, laryngeal preservation rates and voice outcomes?

INTRODUCTION

Cancer of the glottis, the region of the larynx that contains the true vocal cords, is the most common noncutaneous malignancy of the head and neck [1]. An estimated 1,150 new cases of laryngeal cancer will be diagnosed in Canada in 2011, with men being four times more likely to develop the disease than women [2]. While the incidence rates of larynx cancer are significantly decreasing for both men and women, an estimated 490 Canadians are still expected to succumb to the disease this year [2]. The decreasing incidence and mortality rates reflect a decrease in the use of proven risk factors for the disease, specifically tobacco and alcohol use.

Treatment options for early glottic cancer include transoral microsurgery (with or without laser), radiotherapy or, infrequently, open surgery. Regardless of the treatment modality, the goal remains to cure, while avoiding total laryngectomy [3]. Additional goals include maintaining voice quality, minimizing the risk of serious complications and minimizing costs [4].

There is continuing debate about whether radiation therapy or surgery, with or without laser, is the superior treatment for early glottic cancer. The evidence to date has been insufficient to resolve the controversies, particularly because of the paucity of prospective randomized trials. Furthermore, opinions about optimal therapy have been demonstrated to vary across disciplines [1] and between countries [5]. The purpose of this systematic review and evidence-based guideline is to systematically review reported studies in the literature,

compare outcomes among these studies, and provide guidance on the effectiveness of the two most common treatment options for early glottic cancer: endolaryngeal surgery and radiotherapy.

METHODS

The evidence-based series (EBS) guidelines developed by the PEBC, (CCO), use the methods of the Practice Guidelines Development Cycle [6]. For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by two members of the PEBC Head and Neck Cancer Disease Site Group (DSG) (see Appendix 1 for a complete list of DSG members) and one methodologist.

The body of evidence in this review is comprised primarily of retrospective comparative and cross-sectional studies. That evidence forms the basis of the recommendations in Section 1 developed by the Head and Neck Cancer DSG. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care, and all work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

The literature was searched using MEDLINE (OVID: 1996 through December Week 4, 2010), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations (January 10, 2011), EMBASE (OVID: 1996 through January 2011, Week 1), and the Cochrane Library (OVID: 4th Quarter 2010). In addition, the proceedings of the meetings of the American Society of Clinical Oncology (ASCO), the American Society of Therapeutic Radiology and Oncology (ASTRO), and the Canadian Association of Radiation Oncology (CARO) were all searched for relevant abstracts in the years 2007 to the most recently available, 2010. Reference lists of studies deemed eligible for inclusion in the systematic review were scanned for additional citations.

The literature search of the electronic databases combined disease-specific terms (squamous cell carcinoma, cancer, malignancy, neoplasm, tumour) along with site-specific terms (larynx, vocal cord, glottis, subglottic, supraglottic) and treatment-specific terms (irradiation, radiotherapy, surgery, endoscopic surgery, microsurgery) for all study designs (Appendix 2).

In addition to this search of the electronic databases, an Internet search of Canadian and international health organizations and the National Guidelines Clearinghouse was conducted for existing guidelines and systematic reviews relevant to our research question. Guidelines were included if they were published since 2006 in English. This environmental scan yielded three practice guidelines [3,7,8] and one consensus statement [9]. The Working Group of the Head and Neck Cancer DSG decided that proceeding with a new systematic review that includes the latest research was warranted, given the time elapsed or lack of reporting of the literature included in these practice guidelines.

Study Selection Criteria

Inclusion Criteria

Articles were eligible for inclusion in this systematic review of the evidence if they were the following:

- Abstracts or full reports of randomized trials or non-randomized comparative studies that evaluated endolaryngeal surgery, with or without laser, and radiation therapy in the primary treatment of early (T1) glottic cancer.
- Reports of systematic reviews or evidence-based guidelines with systematic reviews that addressed the guideline question.
- Retrospective or cross-sectional studies that included a minimum of 50 patients.

- Studies including patients with greater than T1 disease if the majority of patients had T1 disease and if the outcome of interest was other than post-treatment voice quality.
- Studies reporting at least one of the following outcomes: survival, local or locoregional control, larynx preservation rate, or post-treatment voice quality.

Exclusion Criteria

Articles published in languages other than English were excluded because of limited translation resources.

Quality Appraisal

Systematic reviews and meta-analyses were assessed for quality using the Assessment of Multiple Systematic Reviews (AMSTAR) tool [10]. The quality of primary studies included assessments for study design, type of data collection, balance between the treatment groups, differences in baseline patient characteristics, and reporting of such differences.

Synthesizing the Evidence

If clinically homogenous data from two or more studies are available, the data will be pooled using the Review Manager software [11]. Pooled adjusted hazard ratios (HRs) for survival would be obtained using a random effects model. The presence of statistical heterogeneity would be evaluated using the x^2 test for heterogeneity and the I^2 percentage. A probability level for the x^2 statistic less than or equal to 10% ($p \leq 0.10$) and/or an I^2 greater than 50% would be considered indicative of statistical heterogeneity.

RESULTS

Literature Search Results

A total of 1,045 studies were identified in the complete literature search, of which 146 were pulled for full-text review. The two systematic reviews, one with a meta-analysis, and 17 primary studies that met the inclusion criteria are included in this review. (See Appendix 3 for the flow diagram of search results). Abstracts are not used in PEBC guidelines.

Study Design and Quality

The one meta-analysis [12] was assessed for methodological quality using the AMSTAR tool [10] and received a moderate overall rating, with possible issues around the quality assessment of included studies. The publication did not include a literature search strategy nor report on a priori methods of assessment of included studies. Without such documentation, the methodological rigour could not be adequately assessed. The systematic review by Dey et al [13] was also assessed for quality using the AMSTAR tool [10] and did not suffer from any methodological shortcomings.

Fifteen cohort studies and two cross-sectional studies were included in this review (Table 1). Data collection occurred prospectively in three studies [14-16] and retrospectively in fourteen. Six studies [15-20] had a disproportionate number of patients in one treatment group, while 10 showed a balance between treatment groups. One study [21] did not report the number of patients included in the radiotherapy group and, as such, balance between treatment groups could not be determined. Sixteen of the included studies reported on baseline characteristics. Of these, nine [16,18,20,22-27] specifically tested for differences between treatment groups and reported having done so, and two found significant differences [22,27]. While the remaining seven studies failed to discuss any existing differences in baseline characteristics, balance between treatment groups appears to have been attained in five of these studies [14,15,17,19,28].

Synthesizing the Evidence

Pooling of the study results was deemed inappropriate due to both the lack of adequately designed studies and the heterogeneity that exists between the different study populations and modalities based on the year of administration. Instead, results of each study are presented individually in a descriptive fashion. Where statistical analyses were not reported in a study, the authors of this guideline executed their own analyses of the data, using the statistical software package STATA version 11 [29]. Proportions were compared using a χ^2 test for values greater than 5 and the Fisher's Exact Test for values less than or equal to 5. Values of $p<0.05$ were regarded as significant. The analyses conducted by the authors are distinguished from those reported in the papers by an asterisk (*), which appears next to the p-value in the tables.

Table 1: Included primary studies.

Study	Design	Years	N	Patients	Demographics	Treatment (n)	Follow-up
Brandenburg 2001 [28]	Comparative retrospective study	1989-1999	74	T1N0 carcinoma in situ excluded	**RT group** Age= median 63.2 Male= 86.4% **Sx group** Age= median 64.5 Male= 90%	RT (44) Endoscopic laser Sx (30)	1-11 yrs (median 5.3 yrs)
Bron et al. 2001 [23]	Comparative retrospective study	1983-1996	156	T1-T2 T1a n=43 RT, 39 Sx T1b n=12 RT, 5 Sx T2 n=26 RT, 31 Sx	**RT group** Age= median 64 Male= 85.2% **Sx group** Age= median 61 Male= 85.3%	RT (81) Cold instrument or CO2 laser Sx (75)	NR
Dinapoli et al, 2010 [24]	Comparative retrospective study	1994-2001	143	T1a n=109 T1b n=17 Staging not available n=17	**RT group** Age at dx: median 64.5 Male: 91.4% **Sx group:** Age at dx: median 63 Male= 95.9%	RT (70) CO2 laser Sx (73)	NR
Foote et al, 1997 [17]	Comparative retrospective study	1982-1993	322 (in 3 treatment arms, RT transoral Sx, and open Sx) 163 pts in just the RT and endoscopic Sx arms included here	RT group n=57: CIS n=4 T1a n=18 T1b n=16 T2a n=11 T2b n=4 T3 n=4	**RT group** Age= median 68 (36-88) Male= 96.5% **Transoral Sx group** Age male = median 64.9 (35.5-83.1) Age female = median 67.6 (40.9-77.6) Male= 93.4%	RT (57) Transoral endoscopic Sx (106)	Median 43 months (26-160)
Kujath et al, 2011 [30]	Comparative retrospective study	2000-2009	97	T1 and T2 glottic carcinoma	mean age NR RT: male 87% T1 - 60% CO2 Laser Sx: male 87% T1 - 96%	RT (46) Laser Sx (51)	RT=median 27 mo CO2 laser = median 36 mo

Study	Design	Years	N	Patients	Demographics	Treatment (n)	Follow-up
Mahler et al, 2010 [27]	Comparative retrospective study	1986-2005	351	T1a glottic carcinoma	Age= mean 66 (31-90) Males = 91%	RT (163) Laser Sx (188)	Mean RT: 117 mo (2-261) Sx: 70 mo (4-146)
Oridate et al, 2009 [15]	Comparative prospective study	2006-2007	53	T1 glottic cancer	Age (median): RT: 71 Sx: 79 p=0.01	RT (43) Laser Sx (10)	Median: RT: 6 mo Sx: 24 p=0.007
Osborn et al, 2011 [18]	Comparative retrospective study l	2004-2009	57	Tis and T1a glottic SCC	RT: Age - 69.9 Male- 85.3% Sx: Age – 65.4 Male – 82.6%	RT (34) Tansoral laser Sx (23)	RT: 27.15 mo (1-60) SX: 19.78 mo (1-58)
Peeters et al, 2004 [14]	Cross-sectional	1992-2001	92 of 102 pts completed questionnaire	T1a glottic cancer	RT: mean age=64 (44-83) Male=95% Sx: mean age=66(34-87) Male=90.4%	RT (40) Endoscopic Sx (52)	NA
Rosier et al, 1998 [25]	Comparative retrospective study	1979-1995	72	T1N0M0	Age= median 64 (43-88) Male= 88%	RT (41) Transoral endoscopic Sx (31)	Median 63.5 months (3-194)
Schrijvers et al, 2009 [22]	Comparative retrospective study	1990-2004	100	T1aN0M0	**RT group** Age= median 67 (41-83) Male= 88% **Sx group** Age= median 64 (38-83) Male= 88%	RT (51) CO2 laser Sx (49)	RT=64 mo (12-166) CO2 laser Sx=41 mo (1-119)
Scola et al, 1999 [21]	Comparative retrospective study	1962-1996	80 endoscopic laser resection but RT pts NR	T1-T3	NR	RT (NR) Endoscopic laser excision (80)	NR

Study	Design	Years	N	Patients	Demographics	Treatment (n)	Follow-up
Sjogren et al, 2008 [26]	Comparative retrospective study	since 1996	181	T1 glottic carcinoma T1a n= 143 T1b n=38	RT: T1a mean age=70 (33-89) Male=95.7% Sx: T1a mean age=70 (37-89) Male=89.0% All T1b mean age=70 (46-95) Male=89.5%	RT (72) Laser Sx (109)	Mean 57 months (60 if only living pts were considered)
Smith et al, 2003 [16]	Cross-sectional	1990-2000	55 of 101 pts completed questionnaires	Tis-T1	NR	RT (11) Endoscopic excision (44)	NA
Spector et al, 1999 [20]	Comparative retrospective study	1971-1990 for sx 1971-1985 for low dose RT 1986-1995 for high dose RT	659	T1N0M0	Age= mean 61 (24-93) Male= 88%	RT=194 (low dose 90, high dose 104) Conservation Sx=404 Endoscopic tumour resections=61	Minimum of 3 years
Stoeckli et al, 2003 [31]	Comparative retrospective study	1990-1998	140	Early (stage I and II) glottic carcinoma T1 n=101 T2 n=39	Age= mean 63 (41-88) Male= 94.3%	RT n=75 (45 T1, 30 T2) Laser Sx n=65 (56 T1, 9 T2)	RT: mean 70 months (12-137) Sx: mean 60 months (10-125)
Thurnher et al, 2008 [19]	Comparative retrospective study	1948-1997	337	T1aN0M0	**RT group** Age= median 64 (28-88) Male= 89.8% **Laser Sx group** Age= median 62.7 (34-90) Male= 91.3% **Conventional Sx group** Age= median 63.3 (29-80) Male= 93.2%	RT (108) Conventional Sx (148) Laser excision (81)	Mean 133.8 months

Abbreviations: RT=radiotherapy; Sx=surgery; CO2=carbon dioxide; mo=months; NR=not reported

Outcomes: Oncologic Outcomes

Survival

One recent systematic review by Dey et al. [13], an update of a Cochrane Review first published in 2002, included only randomized controlled trials (RCTs) that compared open surgery, endolaryngeal resection and/or radiotherapy. Only one RCT, published in 1990, that included an adequate number of patients with early glottic cancer was identified. Ogoltsova et al [32] found that five-year survival for T1 tumours was 100% in those undergoing surgery and 91.7% in the radiotherapy group. Disease-free survival at five-years in T1 tumours was 100% following surgery and 71.1% following radiotherapy. Neither of these differences was statistically significant. However, Dey et al [13] reported that the trial was compromised by both methodological and analytical deficiencies and, as such, deemed the evidence insufficient to guide management decisions. Concerns about the methodology of this trial included randomization that was possibly not concealed, the unbalanced number of patients in each group, inadequate staging prior to treatment, poor follow-up, and treatment regimens that were not standardized and likely suboptimal [13].

A recent meta-analysis by Higgins et al [12] compared oncologic outcomes of external radiation to transoral laser surgical excision in the treatment of early glottic cancer. When the laryngectomy-free survival data from four head to head comparison studies were pooled, a trend favouring CO2 laser over radiation therapy was revealed (OR, 0.73; 95% CI, 0.39 to 1.35). However, these results were not statistically significant.

Eleven primary studies reported survival outcomes in patients treated with radiotherapy versus those treated with surgery, with or without laser, for early glottic cancer (Table 2). No significant difference in overall or disease-free survival was detected between the different treatment modalities.

When considering cause-specific death from laryngeal cancer, Thurnher et al [19] found significantly higher mortality in the RT group than in those undergoing surgery (HR, 9.89; 95% CI, 2.16 to 45.39, p=0.0032). The authors attributed this difference to additional and earlier relapses in the RT patients compared to the surgical group. Mahler et al. [27], however, found no significant difference. Survival outcomes appear in Table 2.

Table 2. Survival outcomes

Study	Treatment (n)	Overall Survival Rate	Disease-Free Survival Rate	Cause-Specific Survival Rate
Brandenburg 2001 [28]	RT (44) Endoscopic laser SX (30)	NR	NR	RT= 95.5% SX=100% p=0.511*
Bron et al. 2001 [23]	RT (81) Cold instrument or CO2 laser (75)	RT= 77% SX=70% p=0.324*	NR	**@ 5 yrs** RT= 93% SX=93% p=1.0*
Dinapoli et al, 2010 [24]	RT (70) CO2 laser SX (73)	HR=1.1093 (95% CI=0.3993-3.2976) p=0.7983 HR>1 favours RT	HR=0.9309 (95% CI=0.299-2.8836) p=0.8979 HR<1 favours Sx	NR
Mahler et al, 2010 [27]	RT (163) Laser Sx (188)	RT= 72% SX=78% p=0.285	NR	RT= 97.2% SX=98% p=0.582
Osborn et al, 2011 [18]	RT (34) TLM (23)	RT: 88.2% TLM: 91.3% p=0.89	NR	NR
Rosier et al, 1998 [25]	RT (41) transoral endoscopic sx (31)	RT=74% laser microsx=74% p=0.922*	NR	NR

Study	Treatment (n)	Overall Survival Rate	Disease-Free Survival Rate	Cause-Specific Survival Rate
Schrijvers et al, 2009 [22]	RT (51) CO2 laser sx (49)	No statistically significant difference in overall survival between the 2 groups p=0.679	NR	NR
Scola et al, 1999 [21]	RT(NR) Endoscopic laser resection (80)	**NR**	Endoscopic laser resection: 87.2% RT: 90.4%¶	NR
Spector et al, 1999 [20]	Low dose RT (90) High dose RT (104) Conservation Sx (404) Endoscopic tumour resections (61)	RT low dose = 72% RT high dose = 83% Conservation Sx = 84% Endoscopic resection = 84% High-dose RT and Sx not signif different p=0.365	NR	NR
Stoeckli et al, 2003 [31]	RT (75) Sx (65)	**@ 2 yrs:** RT=98% Sx=96% p>0.05 **@ 5 yrs:** RT=88% Sx=85% p>0.05	NR	**@ 2 yrs:** RT=98% Sx=96% p>0.05 **@ 5 yrs:** RT=93% Sx=96% p>0.05
Thurnher et al, 2008 [19]	RT (108) Conventional Sx (148) Laser excision (81)	**@ 5 yrs:** RT=69% Laser Sx=75% Convent Sx=78% p=0.244 **@ 10 yrs:** RT=52% Laser Sx=53% Convent Sx=57% p=0.151 **@ 15 yrs:** RT=33% Laser Sx=38% Convent Sx=31% p>0.05	NR	**@ 5 yrs:** RT=96% Laser Sx=100% Convent Sx=100% p>0.05 **@ 10 yrs:** RT=92% Laser Sx=100% Convent Sx=98% p>0.05 **@ 15 yrs:** RT=91% Laser Sx=100% Convent Sx=98% p=0.003*

Abbreviations: RT=radiotherapy; Sx=surgery; CO2=carbon dioxide; TLM=transoral laser microsurgery; NR=not reported; yrs=years

*p-value calculated using Chi-square or Fisher's Exact Test in STATA

¶p-value cannot be calculated because the number of patients in the RT group was not available

Locoregional Control

One meta-analysis and ten additional primary studies not included in the meta-analysis reported local control or recurrence rate (Table 3).

In the meta-analysis of 6 direct head-to-head comparisons, Higgins et al [12] found no statistically significant difference in local control between radiation therapy and laser surgery (OR, 0.66; 95% CI, 0.41 to 1.05). Similarly, seven primary studies [18,21-23,26,27, 31] found no significant difference in the local control rate between surgical or radiation therapy patients. However, Foote et al [17] reported a 100% local control rate in radiotherapy patients versus 88% in surgical patients (p=0.004). In considering only T1a patients, Sjogren et al [26] found a marginally significant difference at five years, where 89% of surgical patients experienced local control versus 75% of radiotherapy patients (p=0.05). Statistical testing of

the data from Scola et al [21] was not possible because the number of patients in the radiation therapy group was not reported.

Five studies [19,21-23,28] specifically considered local recurrence rates as an outcome of interest. A significant difference favouring surgery was calculated by the authors of this systematic review from the data of Thurnher et al [19] ($p<0.0001$). However, analyzing the data from Brandenburg [28], Bron et al [23] and Schrijvers et al [22] found no such difference between the surgical and radiation therapy treatment groups. Again, statistical testing of the data from Scola et al [21] was not possible because of lack of reporting. These results appear in Table 3.

Table 3. Control rates and recurrence.

Study	Treatment	Control Rate	Recurrence Rate
Meta-analysis **Higgins et al, 2009 [12]**	RT (459 from 6 studies) CO2 (376 from 6 studies)	Odds Ratio: 0.66 (0.41-1.05) OR<1 favours RT	NR
Brandenburg 2001 [28]	RT (n=44) Endoscopic laser SX (n=30)	NR	RT= 20.5% SX=16.7% p=0.769*
Bron et al. 2001 [23]	RT (n=81) SX (n=75) - cold instrument or CO2 laser	**@ 5 yrs** RT= 77% SX=84% p=0.316*	RT= 18.5% SX=14.7% p=0.668*
Foote et al, 1997 [17]	RT = 57 Transoral endoscopic Sx = 106	RT: 100% Transoral endoscopic Sx: 88% p=0.004*	NR
Mahler et al, 2010 [27]	RT= 163 (treated btw 1986-1995) Laser Sx=188 (treated btw 1996-2006)	**@ 5 yr** RT= 95% SX=92% p=0.395	NR
Osborn et al, 2011 [18]	RT=34 TLM=23	RT: 91.2% TLM: 91.3% p=0.72	NR
Schrijvers et al, 2009 [22]	RT=51 CO2 laser sx=49	**@ 5 yrs** RT= 73% SX=71% p=0.267	RT= 24% SX=27% p=0.908*
Scola et al, 1999 [21]	RT n=NR Endoscopic laser resection n=80	RT= 85.1% Endoscopic laser resection = 97.3%¶	RT= 27.3% Endoscopic laser resection = 11.9%¶
Sjogren et al, 2008 [26]	RT: T1a n=70, T1b n=2 Sx: T1a n=73, T1b n=36	**@ 5 yrs (total cohort)** RT: 79% Sx: 90% p=0.06 **@ 5 yrs (T1a only)** RT: 75% Sx: 89% p=0.05	NR

Study	Treatment	Control Rate	Recurrence Rate
Stoeckli et al, 2003 [31]	RT=75 (45 T1, 30 T2) Sx=65 (56 T1, 9 T2)	**For T1 only @ 2 yrs:** RT=85% Sx=88% p>0.05 **@ 5 yrs:** RT=85% Sx=86% p>0.05	NR
Thurnher et al, 2008 [19]	RT=108 Conventional Sx=148 Laser excision=81	NR	RT=30.5% Conventional Sx=12.8% Laser excision=9.9% p<0.001*

Abbreviations: RT=radiotherapy; Sx=surgery; CO2=carbon dioxide; NR=not reported; yrs=years; TLM=transoral laser microsurgery

*p-value calculated using Chi-square or Fisher's Exact Test in STATA

¶p-value cannot be calculated because the number of patients in the RT group was not available

Larynx Preservation

Ten studies considered laryngeal preservation rate as an outcome of interest, with five of these studies [19,22,26,30,31] showing a significant benefit favouring surgical patients. Laryngeal preservation rates appear in Table 4.

Mahler et al [27] found a significant difference in total laryngectomy rates between the surgery and radiation groups, with an odds ratio for laryngectomy in radiation therapy patients 13.5 times that of laser treated patients for the first three years after treatment (p=0.001).

Table 4. Laryngeal preservation.

Study	Treatment	Laryngeal Preservation
Brandenburg 2001 [28]	RT (n=44) Endoscopic laser Sx (n=30)	RT= 86% SX=97% p=0.230*
Foote et al, 1997 [17]	RT = 57 Transoral endoscopic Sx = 106	RT: 100% Transoral endoscopic Sx: 92% p=0.051*
Kujath et al, 2011 [30]	RT=46 Laser Sx=51	RT: 86% Laser: 100% p=0.02
Mahler et al, 2010 [27]	RT= 163 (treated btw 1986-1995) Laser Sx=188 (treated btw 1996-2006)	**Laryngectomies:** RT: 9% Laser: 1% p=0.001*
Osborn et al, 2011 [18]	RT=34 TLM=23	RT= 94.1% SX=100% p=0.34
Schrijvers et al, 2009 [22]	RT=51 CO2 laser Sx=49	RT= 77% SX=95% p=0.045

Study	Treatment	Laryngeal Preservation
Sjogren et al, 2008 [26]	RT: T1a n=70, T1b n=2 Sx: T1a n=73, T1b n=36	**Total cohort** RT: 86% Sx: 100% p=0.002 **T1a only** RT: 83% Sx: 100% p=0.001
Spector et al, 1999 [20]	High dose RT= 104 Endoscopic tumour resection=61	RT high dose = 89% Endoscopic resection = 90% p=0.880*
Stoeckli et al, 2003 [31]	RT=75 (45 T1, 30 T2) Sx=65 (56 T1, 9 T2)	RT= 82% SX=96% p=0.022*
Thurnher et al, 2008 [19]	RT=108 Conventional Sx=148 Laser excision=81	RT=84.3% Conventional Sx=91.9% Laser excision=100% p<0.0001*

Abbreviations: RT=radiotherapy; Sx=surgery; CO2=carbon dioxide; TLM=transoral laser microsurgery; NR=not reported; yrs=years
* p-value calculated using Chi-square or Fisher's Exact Test in STATA

Outcomes: Voice and Speech Quality

One meta-analysis and six primary studies not included in the meta-analysis reported post-treatment voice assessments in patients with T1 glottic cancer (Table 5). Six studies performed perceptual voice assessments, one of which used a clinician-rated tool and five of which used patient self-perception tools. The meta-analysis considered the assessment of acoustic and aerodynamic voice parameters.

Clinician Perceptual Analysis

In 18 patients with T1a glottic carcinoma, Rosier et al [25] conducted a perceptual voice rating by speech therapists, who blindly evaluated recorded voices and rated quality on a visual scale. An overall trend towards less hoarseness and breathiness after radiotherapy than after laser microsurgery was reported. However, this difference did not reach statistical significance ($p>0.05$).

Patient Self-perception Analysis

Dinapoli et al [24] reported RT patients scored significantly better on the Global Voice Handicap Index (VHI) than did surgical patients ($p<0.0001$). Patients treated with radiotherapy also had significantly better scores on the physical ($p=0.0023$), functional ($p<0.0001$) and environmental ($p<0.0001$) categories of the VHI. In contrast, Peeters et al [14] reported RT patients scored significantly worse on five of 30 VHI statements than did surgically treated patients. Furthermore, surgical patients also had a significantly better mean VHI score ($p<0.05$).

Utilizing two head and neck specific quality of life questionnaires, Smith et al [16] found no significant difference between treatment groups in patient-reported problems with swallowing, chewing, speech, taste, saliva, pain, activity, recreation, or appearance.

Investigating quality of life outcomes after treatment, Oridate et al [15] found no significant difference in Voice-Related Quality of Life (VRQOL) or VHI-10 scores in patients treated with radiotherapy or laser surgery. Similarly, Osborn et al [18] found no significant difference between laser surgery and radiotherapy-treated patients in either the total VRQOL

score or the social/emotional subscore. However, a trend toward higher scores in the RT group for physical functioning was observed (p=0.05).

Acoustic and Aerodynamic Analysis

Higgins et al. [12] identified nine retrospective comparative studies that considered objective voice outcomes in patients undergoing RT or transoral laser surgery. Pooling of the weighted mean differences significantly favoured the RT patients with respect to Maximum Phonation Time (p<0.00001) and Fundamental Frequency (p<0.00001). Phonation Intensity Range also favoured the RT patients, but the difference was not statistically significant (p=0.54). The perturbation measures of jitter and shimmer, in contrast, significantly favoured the patients undergoing transoral laser surgery (p<0.00001 and p=0.002, respectively).

Table 5: Voice outcomes.

Study	Treatment	Voice outcomes
Dinapoli et al, 2010 [24]	RT: n=70 CO2 laser Sx: n=73	**Voice Handicap Index (VHI)¶** **Sum of each category of the VHI** (all scores better for RT pts): physical p=0.0023 functional p<0.0001 environmental p<0.0001 **Global VHI score** (lower is better) RT=median 4 Sx=median 18 p<0.0001
Oridate et al, 2009 [15]	RT: n=43 Laser Sx: n=10	**V-RQOL Scores**:** **Social/emotional:** RT: 93.9 Laser: 96.3 p=0.66 **Physical:** RT: 91.6 Laser: 90.0 p=0.79 **VHI-10 Score:** RT: 2.86 Laser: 3.30 p=0.82
Osborn et al, 2011 [18]	RT: n=34 Transoral laser microsx: n=23	**V-RQOL Scores**:** **Social/emotional:** RT: 89.4 TLM: 83.1 p>0.05 **Physical:** RT: 90.0 TLM: 80.2 p=0.05 **Overall:** RT: 89.8 TLM: 81.4 p>0.05
Peeters et al, 2004 [14]	RT: n=40 Endoscopic Sx: n=52	**Mean VHI Score¶:** RT=18 Sx=12 p<0.05 -Also, separate VHI statements show that RT pts have higher (worse) scores (p<0.05) than Sx pts on 5 of 30 VHI statements

Study	Treatment	Voice outcomes
Rosier et al, 1998 [25]	RT: n=41 Transoral endoscopic sx: n=31	**Overall satisfaction index¥:** **Hoarseness** RT=36% Laser microsx=54% p>0.05 **Vocal instability** RT=44% Laser microsx=43% p>0.05 **Breathiness** RT=41% Laser microsx=59% p>0.05 **Vocal height** RT=50% Laser microsx=61% p>0.05
Smith et al, 2003 [16]	RT: n=10 Endoscopic Sx: n=30	There were no major differences in UW-QOL-R scores between patients treated primarily with radiation therapy or endoscopic excision p>0.05

¶ The VHI consists of an overall question on the quality of the voice and 30 statements on voice-related aspects in daily life. Summarizing the scores on the 30 statements leads to a total VHI score ranging from 0 to 120. A higher score corresponds to a *worse* voice-related functional status

ᵕThe V-RQOL is a 10-item questionnaire that provides scores in two component domains: social/emotional and physical functioning. A composite of these two scores provides an overall measure of voice-related quality of life. Total scores range from 0 to 100, with a higher score indicating *better* voice-related quality of life.

¥Breathiness is a determination of the turbulent noises in the voice, vocal height is a measure of the voice pitch and vocal instability represents a perturbation due to variability in the vibrating frequency.

ONGOING TRIALS

The US National Institutes of Health's clinical trial registry (http://www.clinicaltrials.gov) was searched on July 14, 2011. Two relevant RCTs were identified and are described in Table 6. In addition, the 2010 Cochrane review by Dey et al [13] listed two further studies in their ongoing trails section that were not identified in our search. These too appear in Table 6.

Table 6. Ongoing randomized trials of surgery versus radiotherapy for early glottic cancer.

Title	Comparison of Voice Quality in Early Laryngeal Cancer Between Surgery and Radiotherapy
Protocol ID	bs-86-01-48-5497, NCT00497588
Date last modified	November 17, 2010
Type of trial	Phase III RCT
Comparison	Radiotherapy vs. Surgery
Primary endpoint	Quality of voice
Accrual	Estimated enrolment 33
Sponsorship	Tehran University of Medical Sciences
Status	Recruiting
Title	Endoscopic Surgery or Radiation Therapy in Treating Patients With Stage 0, Stage I, or Stage II Laryngeal Cancer of the Glottis
Protocol ID	NCT00334997
Date last modified	March 5, 2009
Type of trial	Phase II RCT
Comparison	Endoscopic surgery vs. Laser surgery vs. Radiation therapy
Primary endpoint	Feasibility and patient acceptability
Accrual	Estimated enrollment 50
Sponsorship	University College London Hospitals
Status	Unkown

Title	Radiotherapy versus endolaryngeal laser resection for early stage glottic cancer: a randomized controlled trial - Abdurehim 2009
Author	NR
Date last modified	NR
Type of trial	RCT
Comparison	Radiotherapy vs. Endolaryngeal laser resection
Primary endpoint	Survival Rate
Accrual	NR
Sponsorship	NR
Status	NR

Title	A randomised phase III prospective trial to compare laser surgery and radiotherapy as initial treatments for early glottic cancer – Coman 2003
Author	NR
Date last modified	NR
Type of trial	RCT
Comparison	Laser surgery using CO2 laser vs. Radiotherapy
Primary endpoint	Local control, Voice quality, Swallowing function, Quality of life, Nutrition, Cost of treatment
Accrual	NR
Sponsorship	NR
Status	NR

DISCUSSION

Taking into account the results from two systematic reviews, one with meta-analysis, and 20 primary studies, it becomes apparent that the oncologic outcomes are similar between patients treated with radiotherapy or endolaryngeal surgery, with or without laser. Other factors, including voice quality following treatment and the likelihood of subsequent laryngectomy, thus may be currently more important in treatment decision making for early glottic cancer. The preponderance of the retrospective data would suggest that post-treatment quantitative acoustical and aerodynamic voice measurements may favour radiotherapy but patient perception of voice quality did not demonstrate significant differences between treatment modalities. Laryngeal preservation rates were seen to be higher in patients treated with primary surgery. The likelihood of requiring total laryngectomy at some point in patients initially treated with radiation was consistently higher in retrospective studies that assessed this outcome.

With each treatment modality in the management of early glottic cancer being fundamentally different, there is support for both therapies as primary treatment options [33]. Radiotherapy requires patient cooperation for daily treatment for four to six weeks and re-irradiation is not an option in cases of recurrence. Endolaryngeal surgery requires general anaesthesia which may be contraindicated in some patients [27]. Although not substantiated by the evidence, several other factors are important considerations when deciding between surgery and radiotherapy for early glottic cancer. The location of disease is one factor. Anterior commissure involvement may be a factor that favours a recommendation of radiotherapy over surgery due to a common opinion that voice outcomes are particularly affected. Tumours localized to the midportion of the vocal fold, and where endoscopic accessibility is uncompromised, may be considered ideal candidates for surgery. Such practice patterns may be an important confounding variable in comparison studies, since T1b tumours (anterior commissure involvement) have been shown to be associated with higher rates of local relapse as compared to T1a tumours. Although beyond the scope of this systematic review, cost-utility is an increasingly important factor also being considered.

Several limitations of this systematic review should be noted. Varying inclusion criteria between studies were observed. Some studies excluded patients with carcinoma in situ while others included such patients. Cohen et al [34] found the extent of surgical resections differed

among the studies included in their meta-analysis. The authors surmised that, in an attempt to avoid larger resection, more invasive tumours may have been preferentially treated with radiotherapy, thereby producing lower VHI scores in such treated patients [34]. Particularly in the case of post-treatment voice quality studies, the small sample size of included patients is also of concern.

In general, the Head and Neck DSG places greater weight on results from high quality studies, namely RCTs, when making clinical recommendations. In the absence of such high quality evidence, data from other study designs are considered. The systematic review on the topic of surgery versus radiation therapy in early glottic cancer revealed very little high quality evidence. The available literature on the treatment of early glottic cancer is comprised exclusively of non-randomized data, with the vast majority being retrospective in nature. Such study designs are inherently more susceptible to bias and difficult to compare and interpret. In light of the paucity of high-quality evidence on this topic, and the interest expressed by clinicians for guidance in this area, the Head and Neck DSG proceeded with the collection and inclusions of the best available evidence with respect to the question posed. A rigorous systematic review provided a current and comprehensive evidentiary base, which provided the context and direction for the development of recommendations.

CONCLUSIONS

Carcinoma of the glottis is usually diagnosed in the early phase, and both modalities of treatment have shown high cure rates. However, controversies in the treatment of early glottic cancer remain because of the lack of high-quality prospective analyses comparing endoscopic surgery versus radiotherapy. There is no evidence in favour of one treatment modality when considering likelihood of local control or overall survival. There is a suggestion that radiotherapy may be associated with less measureable perturbation of voice as compared to surgery but no significant differences were seen in patient perception. The likelihood of laryngeal preservation may be higher when surgery can be offered as initial treatment. Future research should focus on conducting RCTs or prospective comparative studies, with ample follow-up time, that focus on functional outcomes of patients with early glottic cancer.

CONFLICT OF INTEREST

None declared.

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For a complete list of the Head and Neck Cancer DSG members, please visit the CCO website at http://www.cancercare.on.ca/

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- **Dr. Eric Winquist,** Medical Oncology, London Health Sciences Centre
- **Dr. John Yoo,** Otolaryngology, London Health Sciences Centre

Appendix 2. Literature search strategy.

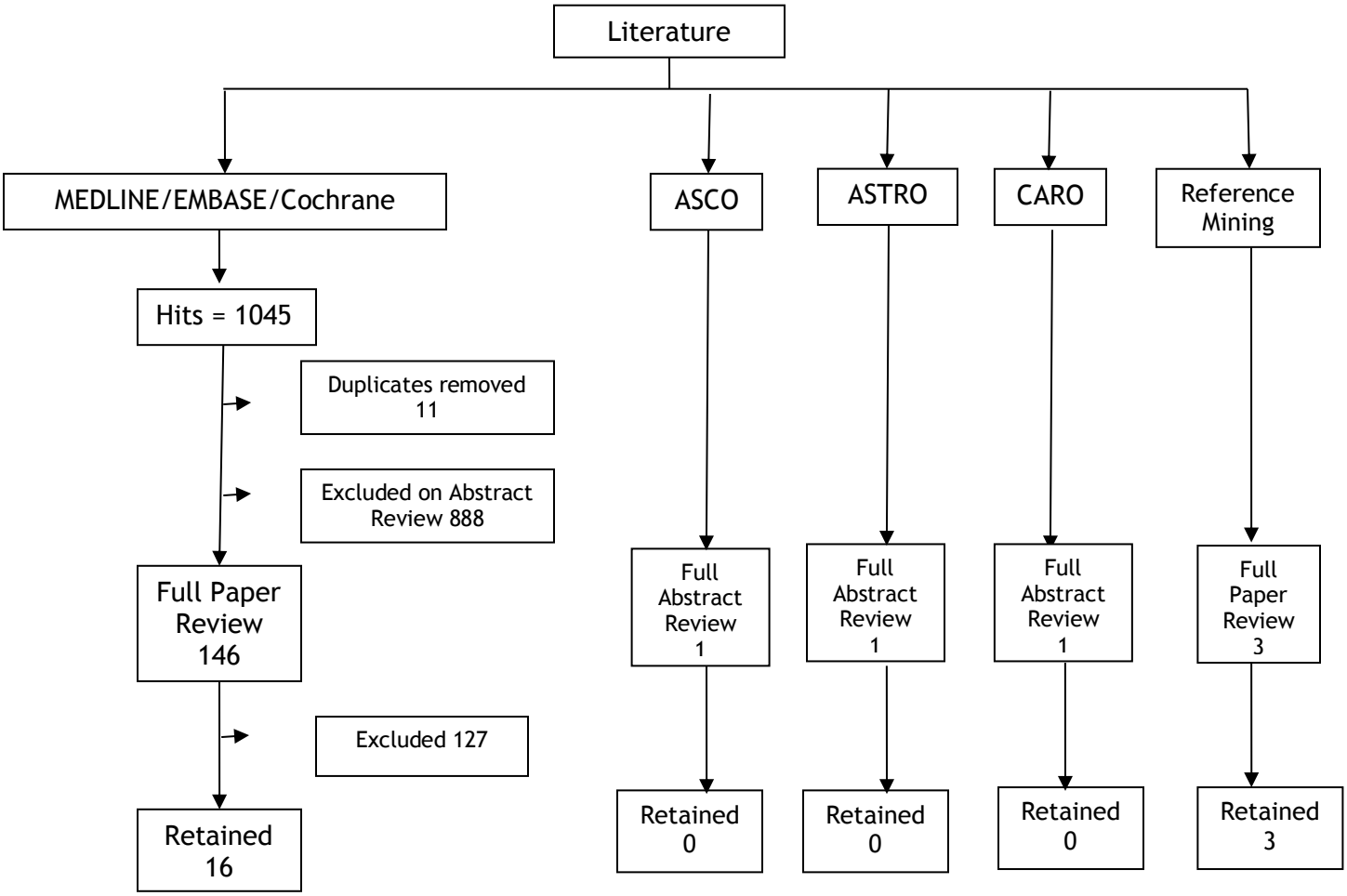
MEDLINE
Database: Ovid MEDLINE(R) <1996 to December Week 4 2010>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <January 10, 2011> Search Strategy:
---
1 exp neoplasm/ (1030587)
2 exp *carcinoma, squamous cell/ (32691)
3 (cancer? or malignan$ or premalignan$ or neoplasm? or carcinoma? or dysplasia or tumo?r?).mp. (1308725)
4 exp larynx/ (11361)
5 (laryn$ or (vocal adj2 cord?) or cordal or glotti$ or throat or (voice adj2 box) or subglotti$).mp. or supraglotti$.mp,tw. (42851)
6 1 or 2 or 3 (1398889)
7 4 or 5 (44458)
8 6 and 7 (14858)
9 exp radiotherapy/ (60826)
10 (irradiat$ or radiotherapy$ or radiation).mp,tw. (241538)
11 exp surgery/ or dissection/ or endoscopic surgery/ or laser surgery/ or microsurgery/ or excision/ (37234)
12 (surgery or surgical? or (laryn$ and preserv$) or laryngectom$ or hemilaryngectom$).mp. (656604)
13 9 or 10 or 11 or 12 (872338)
14 8 and 13 (7810)
15 exp comparative study/ (774361)
16 14 and 15 (782)
17 (case report$ or editorial$ or comment$ or letter$ or news or notes or books).pt. (1369327)
18 16 not 17 (765)
19 limit 18 to (english language and humans) (573)
****

EMBASE
Database: EMBASE <1996 to 2011 Week 01>
---
1 exp neoplasm/ (1459779)
2 exp squamous cell carcinoma/ (47329)
3 (cancer: or malignan: or premalignant: or neoplasm: or carcinoma: or dysplasia or tumo?r: or precancer:).mp,tw. (1635844)
4 exp larynx/ (12960)
5 (larynx: or (vocal adj2 cord:) or cordal or glott: or throat or (voice adj2 box) or subglotti: or supraglotti:).mp,tw. (50014)
6 exp larynx disorder/ (26865)
7 1 or 2 or 3 (1827868)
8 4 or 5 or 6 (54911)
9 7 and 8 (19840)
10 exp larynx tumor/ (10752)
11 9 or 10 (19840)
12 exp radiotherapy/ (166215)
13 (irradiat* or radiotherap* or radiation).mp,tw. (369408)
14 exp surgery/ or exp EAR NOSE THROAT SURGERY/ or exp Larynx surgery/ or dissection/ or exp endoscopic surgery/ or exp laser surgery/ or exp microsurgery/ or exp excision/ (1570806)
15 12 or 13 or 14 (1843386)
16 11 and 15 (11111)
17 (case report$ or editorial$ or comment$ or letter$ or news).pt. (695968)
18 16 not 17 (10670)

19 exp comparative study/ (479826)
20 18 and 19 (604)
21 limit 20 to (english language and humans) (461)
****

COCHRANE
Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2010>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to December 2010> Search Strategy:
---
1 exp neoplasm/ (34244)
2 exp squamous cell carcinoma/ (1648)
3 (cancer: or malignan: or premalignant: or neoplasm: or carcinoma: or dysplasia or tumo?r: or precancer:).mp,tw. (60815)
4 exp larynx/ (376)
5 (larynx: or (vocal adj2 cord:) or cordal or glott: or throat or (voice adj2 box) or subglotti: or supraglotti:).mp,tw. (2775)
6 exp larynx disorder/ (0)
7 1 or 2 or 3 (64722)
8 4 or 5 or 6 (2853)
9 7 and 8 (585)
10 exp larynx tumor/ (0)
11 9 or 10 (585)
12 exp radiotherapy/ (3658)
13 (irradiat* or radiotherap* or radiation).mp,tw. (14890)
14 exp surgery/ or exp EAR NOSE THROAT SURGERY/ or exp Larynx surgery/ or dissection/ or exp endoscopic surgery/ or exp laser surgery/ or exp microsurgery/ or exp excision/ (2790)
15 exp surgery/ or exp EAR NOSE THROAT SURGERY/ or exp Larynx surgery/ or dissection/ or exp endoscopic surgery/ or exp laser surgery/ or exp microsurgery/ or exp excision/ (2790)
16 12 or 13 or 14 or 15 (17517)
17 11 and 16 (276)
18 (case report$ or editorial$ or comment$ or letter$ or news).pt. (7018)
19 17 not 18 (275)
20 limit 19 to yr="1996 -Current" (176)

Appendix 3. Results of the literature search.



cancer care ontario | action cancer ontario
program in evidence-based care | programme de soins fondé sur des preuves

Evidence-Based Series 5-2: Section 3

The Role of Endolaryngeal Surgery (With or Without Laser) versus Radiotherapy in the Management of Early (T1) Glottic Cancer: EBS Development Methods and External Review Process

J. Yoo, C. Lacchetti, A. Hammond, R. Gilbert,
and the Head and Neck Cancer Disease Site Group

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: March 14, 2012

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-Based Series

Each EBS is comprised of three sections:

- *Section 1: Guideline Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation

by the Group or Panel involved and a formalized external review in Ontario by review participants.

- *Section 2: Evidentiary Base*. Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: EBS Development Methods and External Review Process*. Summarizes the EBS development process and the results of the formal external review of the draft version of Section 1: Guideline Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This EBS was developed by the Head and Neck Cancer DSG of the CCO PEBC. The series is a convenient and up-to-date source of the best available evidence on the role of endolaryngeal surgery (with or without laser) versus radiotherapy in the management of early (T1) glottic cancer, developed through review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario.

Report Approval Panel Review and Approval

Prior to the submission of this EBS draft report for External Review, the report was reviewed and approved by the PEBC Report Approval Panel, a panel that includes oncologists and whose members have clinical and methodological expertise. Key issues raised by the Report Approval Panel and the modifications made by the Head and Neck DSG (indicated by ➢) are listed below:

1. Although it is clear for the main users of this guideline, other non-content-expert users may have difficulty with the fact that laryngeal cancer and glottic cancer are used interchangeably.
   - ➢ The first paragraph now outlines the glottis as the region of the larynx that contains the true vocal cords, and glottic remains the term used through the document.
2. It is unclear from the guideline or the website who the authors and collaborators are.
   - ➢ Appendix 1 now outlines all members of the Head & Neck DSG, their affiliations, and disciplines.
3. It should be stressed in the Recommendations that no well designed, prospective, randomized trials have been published to help provide strong, unequivocal recommendations and that the following recommendations are based largely on retrospective, lower quality data.
   - ➢ The following has been added to the qualifying statement: There is currently no well designed, prospective, randomized controlled trial (RCT) that compares endolaryngeal surgery and radiation therapy. Thus, these recommendations are largely based on other comparative study designs.
4. Some of the recommendations/statements are a bit too strong for the quality/quantity of the data and may require some rewording.
   - ➢ In the last paragraph of the Discussion, “provided an ABUNDANT evidentiary base” was replaced with “a current and comprehensive evidentiary base” and the last sentence of Conclusions, “WAS ASSOCIATED” was changed to “MAY BE associated”.
5. The first sentence of the Qualifying Statement: "RT requires long-term cooperation and tolerance and it is a once only application technique", is too indistinct and should be revised.

- This sentence has been modified to now read, "Radiotherapy requires patient cooperation for daily treatment for four to six weeks and re-irradiation is not an option in cases of recurrence."

6. Some emphasis is put on the improvement in cause-specific mortality observed at 15 years in the Thurner et al paper. There are concerns about this being a real phenomenon when no hint of an improvement was seen at 5 or 10 years.
   - The statistically significant result seen at 15 years was something the authors attributed to additional and earlier relapses in the RT patients compared to the surgical group. This statement has now been added.
7. Although no conflicts are declared, it should be explored as to whether the various techniques used can lead to income differentials large enough to potentially cause the appearance of conflict.
   - Financial interests from professional income are indeed considered in the PEBC's Conflict of Interest Form. No conflicts were declared.
8. The guideline question describes 3 outcomes: locoregional control, laryngeal preservation rates and voice outcomes. The actual outcomes reported in table 2 are OS, DFS and CSS. Suggest changing first outcome in guideline question to "oncologic outcomes" or spelling out OS, DFS and CSS to better align the question with the synthesized data.
   - Survival has now been added as an outcome of interest.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and the review and approval of the report by the PEBC Report Approval Panel, the Head and Neck Cancer DSG circulated Sections 1 and 2 to external review participants for review and feedback. Box 1 summarizes the draft recommendations and supporting evidence developed by the DSG.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review 2012-01-12)
QUESTION

In patients with early (T1) glottic cancer, what is the role of endolaryngeal surgery (with or without laser) versus radiation therapy, in terms of survival, locoregional control, laryngeal preservation rates and voice outcomes?

TARGET POPULATION

The target population of this guideline is adult patients with previously untreated early (T1) glottic cancers.

INTENDED USERS

This guideline is intended for use by clinicians and healthcare providers involved in the management or referral of adult patients with early (T1) glottic cancer.

RECOMMENDATION

For patients with early (T1) glottic cancer, recommended treatment options include the equally effective endolaryngeal surgery, with or without laser, or radiation

therapy. The choice between treatment modalities should be based on patient and clinician preferences and general medical condition.

QUALIFYING STATEMENT

There is currently no well-designed, prospective, randomized controlled trial (RCT) that compares endolaryngeal surgery and radiation therapy. Thus, these recommendations are based primarily on other comparative study designs. Although not substantiated by the evidence, several factors are important considerations when deciding between surgery and radiotherapy for early glottic cancer. Location of disease is one factor. Anterior commissure involvement may be a factor that favours a recommendation of radiotherapy over surgery due to a common opinion that voice outcomes are particularly affected. Tumours localized to the midportion of the vocal fold, and where endoscopic accessibility is uncompromised, may be considered ideal candidates for surgery. Other important practical considerations include the ability for patients to tolerate a general anaesthetic, which is required for surgery. In contrast, radiotherapy requires patient cooperation for daily treatment for four to six weeks. Partial laryngeal surgery, including revision endoscopic surgery, is possible for local recurrence following surgery. However, re-irradiation is not an option in cases of recurrence.

KEY EVIDENCE

There is a lack of high-quality evidence to explicitly inform the guideline question. Notwithstanding, the recommendation is based on the best available evidence and a consensus of expert clinical opinion of the Head and Neck Cancer Disease Site Group.

One meta-analysis, fifteen cohort studies and two cross-sectional studies comparing endolaryngeal surgery (with or without laser) to radiation therapy in patients with early glottic cancer comprised the evidence base.

- No statistically significant differences in overall survival or disease–free survival were detected. One retrospective cohort study (1) did report a significant (p=0.003) 15-year cause-specific survival benefit in surgically treated patients (100%) over those treated with radiation therapy (91%). This result was not consistent with four other retrospective cohort studies (2,3-5) that also considered cause-specific mortality and showed no significant differences. The meta-analysis [6] detected no statistically significant laryngectomy-free survival benefits associated with laser surgery when compared to radiation therapy (odds ratio [OR], 0.73; 95% confidence interval [CI], 0.39-1.35).
- One meta-analysis (6) found no statistically significant difference in local control between radiation therapy and laser surgery (OR, 0.66; 95% CI, 0.41 to 1.05). One (7) of eight retrospective cohort studies reported a marginally significant better control rate in surgically treated patients (89%) over those treated with radiotherapy (75%) when only T1a patients were considered (p=0.05). One retrospective cohort study [1] also reported a significant difference in recurrence rates favouring surgery. Thurnher et al (1) found a recurrence rate of 30.5% in those undergoing radiation therapy versus 9.9% in the patients treated with laser excision (p=0.001). The remaining five studies did not report any such significant differences in recurrence rates between treatment groups.
- Laryngeal preservation rates were found to be better with surgery, (with or without laser) as compared to radiation in five studies (1,5,7-9), while one study

found a marginally significant better preservation rate with radiation therapy (p=0.051) (10).

- Post-treatment voice and speech quality was assessed by clinician perceptual analysis in one retrospective cohort study (11), which found that the difference between radiation therapy patients and those treated surgically did not reach statistical significance. In five studies that analyzed patient self-perception, three (12-14) found no statistically significant difference between treatment groups, one (15) found radiation therapy patients scored significantly better, and one (16) study reported surgically treated patients scored better. One meta-analysis (6) found conflicting results. It detected significantly better maximum phonation time and fundamental frequency in the radiation therapy patients but reported that the perturbation measures of jitter and shimmer significantly favoured the patients undergoing transoral laser surgery.

Methods

Targeted Peer Review: During the guideline development process, six targeted peer reviewers from Ontario and Alberta, considered to be clinical and/or methodological experts on the topic, were identified by the working group. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Three reviewers agreed and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on August 25, 2011. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The Head and Neck DSG reviewed the results of the survey.

Professional Consultation: Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. All Head and Neck professionals from Ontario in the PEBC database were contacted by email to inform them of the survey. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). The notification email was sent on January 23, 2012. The consultation period ended on March 5, 2012. The Head and Neck DSG reviewed the results of the survey.

Results

Targeted Peer Review: Three responses were received from six reviewers. Key results of the feedback survey are summarized in Table 1.

Table 1. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=3)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.				1	2
2. Rate the guideline presentation.				1	2
3. Rate the guideline recommendations.				1	2

4. Rate the completeness of reporting.				1	2
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?				2	1
6. Rate the overall quality of the guideline report.				2	1
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.				1	2
8. I would recommend this guideline for use in practice.					3

9. What are the barriers or enablers to the implementation of this guideline report?

Limitations of the evidence, institutional treatment bias, possible technical limitations or lack of experience/training in transoral microsurgery at some centres, and access to CO2 laser and microlaryngeal equipment were recorded as potential barriers. Another reviewer thought there would be no such barriers to implementation.

One reviewer suggested that most clinicians already accept the equivalence of the two treatment modalities in this patient population and have the facilities to deliver either modality, thereby enabling the implementation of this guideline.

Summary of Written Comments

The written comments received from the reviewers were predominantly favourable and included positive feedback on the appropriateness of methods used, transparency of the process, organization of the guideline, suitability of the included stakeholders, and quality of the systematic review. Reviewers acknowledged the limitations of the poor quality data and commented on the lack of evidence to support any one treatment modality over the other. Based on the available information, one reviewer suggested both treatment options should be discussed with patients in a multidisciplinary fashion. Finally, a suggestion of conducting a cost-utility analysis was raised. However, with cost analyses outside of the scope of the PEBC guidelines, no modifications were taken based on this feedback.

Professional Consultation: Fifteen responses were received. Key results of the feedback survey are summarized in Table 2.

Table 2. Responses to four items on the professional consultation survey.

	Number (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	1 (6.7)	**0**	4 (26.7)	7 (46.7)	3 (20)

	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	1 (6.7)	**0**	3 (20)	6 (40))	5 (33.3)
3. I would recommend this guideline for use in practice.	1 (6.7)	1 (6.7)	3 (20)	6 (40))	4 (26.7)

4. What are the barriers or enablers to the implementation of this guideline report?

Practitioners listed barriers to the implementation of this guideline, which included the following:

1. **Limitation of the evidence**
   Several practitioners commented that the lack of high quality evidence may act as a barrier to uptake.

2. **Existing biases**
   Many practitioners reported that existing biases based on the discipline of the treating physician could act as a barrier to the implementation of this guideline. Additionally, incorrect patient preconception was suggested as a potential barrier. Some remarked that this guideline will do nothing but reinforces the prejudices already in play amongst the advocates of each treatment modality.

3. **Economic**
   Economic consideration should be given regarding the two treatment modalities to enable the guideline implementation.

4. **Patient suitability**
   Practitioners remarked that not all patients are candidates for laryngeal laser surgery and this may hinder implementation. Criticism over patient selection in the surgery group in the included literature was also commented upon and suggested as a further potential hurdle.

Summary of Written Comments

Three of the fifteen responders to professional consultation provided additional written comments. These included positive feedback on the summary, the need for a large prospective study comparing radiation without salvage surgery to laser surgery, and a comment on the advantage of partial surgery in that it enables future use of XRT in second malignancies.

Modifications/Actions

The majority of the comments received from responding Ontario practitioner are already recognized by the DSG and many are addressed within the evidence-based report. However, with the limitation of the included evidence commented on by many external reviewers, a statement renewing the systematic process taken and the emphasis placed on higher quality evidence when available was added to the discussion. No further modifications to the guideline were taken.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Head and Neck DSG and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Contact Information

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For information about the PEBC and the most current version of all reports, please visit the CCO Web site at http://www.cancercare.on.ca/ or contact the PEBC office at:

Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

REFERENCES

1. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol. 1995;13:502-12. Comment in: Ann Oncol. 2002 Sep;13(9):1507-9; author reply: 1509.
2. Browman GP, Newman TE, Mohide EA, Graham ID, Levine MN, Pritchard KI, et al. Progress of clinical oncology guidelines development using the practice guidelines development cycle: the role of practitioner feedback. J Clin Oncol. 1998;16(3):1226-31.

Ontario Health
Cancer Care Ontario

Evidence-Based Series 5-11 Version 2: Section 4

The Role of Endolaryngeal Surgery (With or Without Laser) versus Radiotherapy in the Management of Early (T1) Glottic Cancer

Document Review Summary

K. Fung, C. Arinze, and the Head and Neck Cancer Guideline Development Group

The 2012 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2012.

In November 2021, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature. A clinical expert (KF) reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed. The Head and Neck Disease Site Group (DSG) endorsed the recommendations found in Section 1 (Clinical Practice Guideline) in October 2023.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered

In patients with early (T1) glottic cancer, what is the role of endolaryngeal surgery (with or without laser) versus radiation therapy, in terms of survival, locoregional control, laryngeal preservation rates and voice outcomes?

Literature Search and New Evidence

The new search (2011 to December 2022) yielded five systematic reviews and 15 primary studies investigating the management of early stage glottic cancer. An additional search for ongoing studies on clinicaltrials.gov yielded two potentially relevant ongoing trials. Brief results of these publications are shown in the Document Summary and Review Tool.

Impact on the Guideline and Its Recommendations
The newly identified evidence supports existing recommendations. For functional outcomes (swallowing, voice outcomes), it is acceptable for the choice between treatment modalities to be based on general medical condition and patient or clinician preferences. However, the systematic review by Huang et al showed that in the T1a subgroup, laryngeal preservation is better with surgery than RT. This finding does not invalidate the recommendation since the current guideline did not recommend one treatment option over the other. However, the clinical expert suggested adding a statement that gives the provider an option in the T1a subgroup based on evidence and clinical practice.

Current recommendation: For patients with early (T1) glottic cancer, recommended treatment options include the equally effective endolaryngeal surgery, with or without laser, or radiation therapy. The choice between treatment modalities should be based on patient and clinician preferences and general medical condition.

October 2023: It is the opinion of the Head and Neck Cancer Guideline Development Expert Panel that the following statement be added:

For patients in the T1a subgroup, treatment with surgery is preferred.

Document Review Tool

Number and Title of Document under Review	5-2 The Role of Endolaryngeal Surgery (With or Without Laser) versus Radiotherapy in the Management of Early (T1) Glottic Cancer
Original Report Date	March 14, 2012
Date Assessed (by DSG or Clinical Program Chairs)	November 16, 2021
Health Research Methodologist	Chika Arinze
Clinical Expert	Dr. Kevin Fung
Approval Date and Review Outcome (once completed)	October 16, 2023

Original Question:
In patients with early (T1) glottic cancer, what is the role of endolaryngeal surgery (with or without laser) versus radiation therapy, in terms of survival, locoregional control, laryngeal preservation rates and voice outcomes?

Target Population:
The target population of this guideline is adult patients with previously untreated early (T1) glottic cancers.

Study Selection Criteria:
Inclusion Criteria

Articles were eligible for inclusion in this systematic review of the evidence if they were the following:

- Abstracts or full reports of randomized trials or non-randomized comparative studies that evaluated endolaryngeal surgery, with or without laser, and radiation therapy in the primary treatment of early (T1) glottic cancer.
- Reports of systematic reviews or evidence-based guidelines with systematic reviews that addressed the guideline question.
- Retrospective or cross-sectional studies that included a minimum of 50 patients.
- Studies including patients with greater than T1 disease if the majority of patients had T1 disease and if the outcome of interest was other than post-treatment voice quality.
- Studies reporting at least one of the following outcomes: survival, local or locoregional control, larynx preservation rate, or post-treatment voice quality.

Exclusion Criteria

Articles published in languages other than English were excluded because of limited translation resources.

Search Details:

- 2011 to December 2, 2022, (Cochrane Database of Systematic Reviews)
- January 2011 to December 5, 2022 (Medline and Embase)
- April 2023 (Clinicaltrial.org for ongoing trials)

Summary of new evidence: Out of 2785 hits from the search of Medline, Embase, and the Cochrane Database for Systematic Reviews, the full text of 66 publications were reviewed and 21articles were retained for inclusion. The included articles represent five systematic reviews and 15 primary studies investigating the management of early stage glottic cancer. An additional search for on-going trials yielded two studies. Clinical Expert Conflict of Interest Declaration: K. Fung and C. Arinze declared no conflict of interest.	
1. Does any of the newly identified evidence contradict the current recommendations? (i.e., the current recommendations may cause harm or lead to unnecessary or improper treatment if followed)	No.
2. Does the newly identified evidence support the existing recommendations?	Yes.
3. Do the current recommendations cover all relevant subjects addressed by the evidence? (i.e., no new recommendations are necessary)	No. The current guideline does not recommend one treatment option over another. Making a statement that gives the provider an option in the T1a subgroup is preferred. There is evidence showing that in the T1a subgroup, laryngeal preservation is better with surgery than RT (Huang et al). For functional outcomes (swallowing, voice outcomes), it is acceptable for the choice between treatment modalities to be based on patient and clinician preferences and general medical condition.
Review Outcome as recommended by the Clinical Expert	ENDORSE (with modification)
If outcome is UPDATE, are you aware of trials now underway (not yet published) that could affect the recommendations?	
DSG/Expert Panel Commentary	

Evidence Tables

Author [Ref#]	Study Design (Med F/U in Months)	Population and number of patients	Result
Wang 2022(1)	Retrospective study Surgery vs. TLM vs. RT Med F/U: 62.9 mos	Clinically node negative early glottic cancer patients. • 8.3% female • Mean age = 52.4 yr. n= 144	• The five-year survival rates are 83.0%, 82.2%, and 82.6% for surgery, LS, and RT respectively. There was no significant difference in the 5yr survival rates (p = 0.987)

Gu 2022(2)	Prospective study
	
	TRM vs. RT
	
	Med F/U = 75.6mos
		Patients with T1 glottic carcinoma
		• ECOG≥ 2
		
		n = 41
			• Swallowing-related QoL was significantly better in the TRM group than in the RT group (P < 0.01)
			  • The overall CSWAL-QOL scores were 864.0 (830.3 to 883.0) vs. 797.7 (784.4–804.2) for the TRM and RT groups, respectively,
			  • The frequency scores were 91.43 (88.6 to 94.3) and 75.7 (73.0 to 78.6) for the TRM and RT groups, respectively.
			
			• The RT group scored significantly better than the TRM group on the Communication dimension. 70.0 (70.0 to 90.0) vs. 90.0 (82.5 to 90.0) P < 0.01
			
			• The two groups had significantly different DS and PAS scores.
			  • The average DS score of the TRM vs. RT group was 1.0 (0.5–3.0) vs. 5.5 (3.2–7.0), (P < 0.01).
			  • The average PAS score of the TRM vs. RT group was 1.0 (1.0–2.0), 4.0 (3.0–6.8), P < 0.01.

Shen 2020(3)	Retrospective Analysis
	
	TLM vs. EBRT
	
	Med F/U = 42mos
		Pathologically confirmed squamous cell carcinoma with T1N0 disease (76.76%) and T2N0 (23.24%)
		• Med age = 62yr
		
		n = 185
			• There were no significant differences between the groups in the:
			  • 3-year LC, 94.1% vs. 96.9% (p=0.750)
			  • 3-year PFS, 93.1% vs. 95.3% (p=0.993)
			  • 3-year OS 95.4% vs. 93.3% (p=0.467),

			• The vocal quality was significant better in the EBRT group compared to the TLM group (p=0.001). The post treatment VHI scores were:
			  • At 6 mos: 19.45±5.112 vs. 10.24±6.093
			  • At 12 mos: and 14.97±7.741 vs 9.45±5.112

Lois-Ortega 2020(4)	Retrospective analysis TLM vs. RT F/U = nr	Patients diagnosed with SCC • Stage 1: 78.% • Mean age = 64.24 yr and 59.31yr for men and women respectively n =164	• There was no significant difference in tumour control between the groups. Both treatments achieved good local control; (84.15% in the TLM and 89.6% for RT) • Treatment with RT showed significantly better laryngeal preservation compared to treatment with TLM: 81.6% vs. 100% (p < 0.001)

Kim 2020(5)	Retrospective analysis of NCDB
	
	Surgery vs. EBRT
	
	Med F/U = 49.5 mos
		Patients with early stage glottic cancer
		
		n = 14,498
			• Those treated with surgery demonstrated significantly improved survival outcomes compared to those treated with RT.
			  • Median survival: 131.3 mos vs.113.5 mos
			  • 5-year OS: 77.5% vs 72.6% (P < 0.0001).
			  • aHR 0.87(95% CI0.81-0.94), P = 0.0004)
			  • When surgery was compared with standard RT regimen (66-70 Gy in 33-35 fractions), the results showed worse survival (aHR 1.15, 95% CI 1.07-1.23, P = 0.0003).
			  • When surgery was compared with hypofractionated RT regimen (63-67.5 Gy in 28-30 fractions), patients undergoing surgery no longer showed improved OS (aHR 0.94, 95% CI 0.86-1.02, P = 0.154).

Du 2020(6)	Retrospective analysis of SEER database Surgery vs. RT	Patients with T1-2N0M0 glottic LSCC n = 6538	• Compared to surgery, patients who received radiation therapy had significantly worse overall survival outcomes compared with patients who underwent surgery (p = 0.0035) • Patients who received radiation also had a higher risk of cancer-specific mortality (p = 0.003)

Gandhi 2018(7)	Retrospective analysis of hospital record
	
	TLS vs. RT
		Patients who were diagnosed with early glottic carcinoma (TIa, TIb) and who underwent either CO2 laser excision or Radiotherapy as primary treatment modality
		n = 60
			• GRBAS and VHI scores for patients who underwent laser cordectomy were found to be significantly better than those who underwent RT in
			  • Grade: 1.15 ± 0.74 vs. 0.63 ± 0.62 (p = 0.01)
			  • Roughness: 0.95 ± 0.82 vs. 0.40 ± 0.54 (p = 0.01)
			  • Strain: 0.45 ± 0.60 vs. 0.10 ± 0.37 (p = 0.02)
			• GRBAS scores were not significant difference in:
			  • Breathiness: 0.75 ± 0.71 vs. 0.48 ± 0.64 (p = 0.13)
			  • Asthenicity: 0.10 ± 0.30 vs. 0.10 ± 0.30 (p = 1.00)
			
			• The subjective findings were confirmed by objective scores generated by the MDVP software for
			  • Jitter: 1.45 ± 0.48 vs.0.87 ± 0.32 (p = 0.01)
			  • Shimmer: 4.25 ± 1.01 vs. 3.60 ± 0.87 (p = 0.01)
			  • NHR scores: 0.22 ± 0.04 vs. 0.17 ± 0.03 (p = 0.05)
			  • Fundamental Frequency: 135 ± 0.75 vs. 132 ± 0.58 (p = 0.16)
			
			• Significant difference was found in the VHI handicap scores were significantly lower in post-op laser cordectomy patients compared to post RT patients
			  • handicap scores: 13 ± 0.67 vs.18 ± 0.93 (p = 0.04)

Peng et al 2016(8)	Retrospective analysis surgery vs. RT or PDT F/U = 2 mos to 160 mos	Early glottic carcinoma patients with pathologic diagnosis of squamous cancer with complete clinical data n = 202	• There was no statistical significance between surgery and RT in OS, DFS and LC. • The laryngeal function preservation rate was significantly better in the RT group compared to Surgery group: 90% vs. 65.1% respectively (P = 0.025). • The laryngeal function preservation rate was significantly better in the PDT group compared to Surgery group: 86.7% vs. 65.1% respectively (P = 0.02). • There is no significant difference between RT group and PDT group (P>0.05)

Kono 2016(9)	LS vs. RT F/U = 12mos	Patients with T1 glottic cancer treated with RT or type II cordectomy n = 64	At 12 months after treatment: • There were no differences between the groups in fundamental frequency, roughness, asthenia, and strain • perceptual scores of grade and breathiness were significantly better in the LS group compared with those in the RT group. • perceptual scores of grade and breathiness were significantly better in the LS group compared with those in the RT group. • RT group was significantly better than the LS group in jitter, shimmer, NHR, and aerodynamic MPT. • Subjective vocal assessment scores measured by VHI and V-RQOL were also significantly better in the RT group than in the LS group

Arias 2015(10)	Cross sectional
	
	Surgery vs. RT.
		disease-free early glottic cancer patients
		n = 91
			• Self-reported voice quality significantly better those treated with RT compared to surgery, reported
			  • emotional functioning (88.5 vs 76.6)
			  • social contact (4.6 vs 12.1)
			  • VHI (6.1 vs 12.8),

Swisher-McClure, 2014(11)	Retrospective analysis of SEER database.
	
	Med F/U = 5.3 years
		Patients diagnosed with pathologically confirmed squamous cell carcinoma of the glottic larynx
		n = 8721
			• The risk of fatal CVA was significantly higher in those treated with EBRT compared to those treated with surgery. The 15yr unadjusted cumulative incidence was
			  • 2.8% (2.3% to 3.4%) vs.1.5% (0.8% to 2.3%) HR 1.72; (1.02–2.89); p = 0.04
			  • Even when adjusted for patient and demographic characteristics, EBRT remained associated with an increased risk of fatal CVA compared to surgery: Adjusted HR, 1.75; 95% CI, 1.04–2.96; p = 0.04.
			• There was no significant difference between the groups in the unadjusted 15-year cumulative incidence of death from non–CVA-related causes: HR = 0.912 (0.77–1.09) p =0.30

			• There was no significant difference between the treatment groups in overall survival HR 1.03 (0.95–1.13) p = 0.48)
Comert 2014(12)	Case series LS vs. RT LS Mean F/U: 29.3 mos RT Mean F/U: 31.7 mos	patients with early stage (T1-T2) glottic carcinoma with no previous history of malignant disease n = 140	• There were no significant differences in LS and RT groups • 3-year LC: 93.1% vs. 89.7%. P = 0.434. • 3-year DFS: 97.4% vs. 97.9%: P = 0.618
Cerezo 2011(13) [ABSTRACT]	Surgery vs. RT follow-up of 73 months	Patients with early glottic cancer n = 160	• There were no significant differences in 5-year DFS among patients treated with surgery (92%) or radiotherapy (84%). • Compared with surgery, no statistically significant differences were found globally. • Mean value of VHI-10 was 0.9 for the radiation group and 1.08 for the surgery group.
Kerr 2012(14)	Multicenter, retrospective consecutive cohort TLM vs RT TLM Med F/U: 28 mos RT Med F/U: 32 mos	Patients treated for early glottic cancer. n = 234	• There were no significant differences between the groups in survival. • 5yr DFS: 99.62% vs. 99.61% • 5yr OS: 91.63% vs. 90.64% • The 2yr laryngeal preservation rate for stage 1 disease was significantly better in TLM compared to RT • 100% vs. 92% (P < 0.004) • TLM patients have poorer voice quality than RT patients
Laoufi 2014(15)	Retrospective study LS vs. RT Med F/U: 3.5 years	Disease-free T1a glottic squamous cell carcinoma patients n = 147 patients	• subjective voice-related quality of life was worse with LS compared to RT • The average total VHI scores for LS vs. RT were 29.2 vs. 13.1 respectively (P < 0.0001) • The speaking sub-score of the EORTC QLQ-HN35 was significantly better in the RT group compared to the LS group (P = 0.04).

Van Gogh 2012(16)	Prospective cohort study
	
	LS vs. RT
	
	Med F/U: 2 years
		male patients with normal mobility glottic cancer that is limited to one vocal fold and has no regional lymph node metastasis or distant metastasis.
		• Mean age: 65.5yrs
		
		n = 106
			• There was no significant difference in 5-year local control.
			• 3mos post treatment: Those treated with LS had significant better scores for jitter (t = −2.9, p = 0.007), shimmer (t = −3.1, p = 0.004) and fundamental frequency (t = 3.8, p = 0.0004)
			  • The significance was not sustained at 6 – 24 mos post treatment.
			• Voices quality after treatment was significantly higher in LS group compared to RT group at
			  • 12 mos (t = 2.3, p = 0.027) and
			  • 24 mos (t = 2.4, p = 0.018)

Systematic Review and Meta-analysis			

Huang (2017a)(17) (2017b)(18)	Systematic review and meta-analysis of 14 studies
	
	LS vs. RT
		Patients who accepted the first treatment for T1a glottic carcinoma with oncologic outcomes, such as larynx preservation, local control, overall survival, and disease-specific survival.
		
		n = 1217
			• There was no statistical difference between the two groups in terms of
			  • LC: OR = 1.08, (95% CI = 0.73–1.60, p = .07),
			  • OS: OR = 1.26, (95% CI = 0.90–1.76, p=.17)
			  • DSF: OR = 1.98, (95% CI = 0.86–4.54, p = .11)
			  • Voice Handicap Index, Jitter, Shimmer, and airflow rate.
			• LS had significantly better larynx preservation compared with RT group,
			  • OR = 3.86, (95% CI = 1.47–10.13, p = 0.006)

Mo et al 2016(19)	Systematic review and meta-analysis
	
	TLM vs. RT
		Studies that assessed the oncologic outcomes and QoL T1 glottic cancer patients.
		
		n = 1238
			• There were no statistically significant differences local control between TLM and RT:
			  • OR = 0.98 (95 % CI 0.7, 1.38; P = 0.91).
			• The laryngeal preservation for patients undergoing TLM was significantly better than that for RT
			  • OR was 5.81 (95 % CI 3.36, 10.05; P < 0.001)
			• The laser surgery significantly improved the overall survival of patients with T1 glottic carcinoma.
			• OR = 1.35; (95 % CI 1.02, 1.79; P = 0.04)

Abdurehim 2012(20)	Systematic review and meta-analysis
	
	TLS vs. RT.
		patients diagnosed with T1a SCC of the glottic larynx following laryngoscopy and biopsy.
		
		n = 1729
			• No significant differences were identified between TLS and RT with respect to
			  • LC: OR of 0.94 (95% CI: 0.57 -1.57) p = 0.83
			  • OS: OR = 1.22; (95% CI: 0.89–1.66) p = 0.21
			  • DSS: (OR =1.60 (95% CI: 0.79– 3.26) p = 0.19
			  • Posttreatment voice quality.
			• larynx preservation was significantly higher in patients initially treated with TL compared to RT
			  • OR 3.11 (95% CI: 1.16 to 8.34) p = 0 .02

Feng,2011(21)	Meta-analysis of 11 studies
	
	LS vs. RT
		Patients with previously untreated early stage glottic cancer
		
		n = 1,135
			• There was no significant difference in local control rate at
			  • 2-year: RR = 0.55, (95% CI: 0.28–1.09)
			  • 3-year: RR = 0.84, (95% CI: 0.48–1.47)
			  • 5-year: RR = 0.90, (95% CI: 0.59–1.39)

CI: confidence interval; CSWAL-QOL: Chinese version of the Swallowing Quality-of-Life Questionnaire; CVA: cerebrovascular accident; DFS: disease-free survival; DS: The dysphagia score; EBRT: external beam radiation therapy; EORTC: European Organization for Research and Treatment of Cancer; EORTC-QLQ-HN35: EORTC Head and Neck Quality of Life questionnaires; GRBAS: Grade, Roughness, Breathiness, Asthenicity, Strain; HR: hazard ratio; LC: local control; LFS: laryngectomy-free survival; LSCC: laryngeal squamous cell carcinomas; NCDB: National Cancer Database; OS: overall survival; PDT: Photodynamic therapy; QLQ-C30: Quality of Life Questionnaire-Core 30-questions; QLQ-H&N35: QLQ-Head and Neck 35-questions; SEER Surveillance, Epidemiology, and End Results; KPS score, TLM: transoral laser microsurgery; TRM: transoral radiofrequency microsurgery; VFSS: videofluoroscopic swallowing study; VHI: Voice Handicap Index

Ongoing Trials

Official Title	Status	Protocol ID	Last Updated
Comparison of Voice Results at 5 Years of Treatment of Glottic Squamous Cell Carcinoma T1 by Surgery Versus Radiotherapy	Completed	NCT04447456	February 6, 2023
Clinical Treatments in Specialized Disease of Laryngeal Carcinoma (LC) and Hypopharyngeal Carcinoma (HPC)	Recruiting	NCT04908696	June 1, 2021

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Appendix 1. Members of the Expert Panel

Name	Affiliation	Conflict of Interest Declaration
Dr. Margaret Anthes	Thunder Bay Regional Health Sciences Centre, Thunder Bay ON	No conflict of interest declared
Dr. Kelvin Chan	Odette Cancer Centre, Toronto, ON	No conflict of interest declared
Dr. Jason Franklin	Kingston General Hospital, Kingston, ON	No conflict of interest declared
Dr. Ralph Gilbert	Toronto General Hospital, Toronto, ON	No conflict of interest declared
Dr. Michael Gupta	St. Joseph's Healthcare, Hamilton, ON	No conflict of interest declared
Dr. Kevin Higgins	Sunnybrook Health Sciences Centre, Toronto, ON	No conflict of interest declared
Dr. Michael Odell	The Ottawa Hospital, Ottawa, ON	No conflict of interest declared
Dr. David Palma	London Health Sciences Centre, London, ON	No conflict of interest declared
Dr. Kenneth Schneider	Windsor Regional Cancer Centre, Windsor, ON	No conflict of interest declared
Dr. Eric Winquist	London Health Sciences Centre, London, ON	No conflict of interest declared

Appendix 2. Search Strategy

Database(s): **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions** 1946 to December 01, 2022
Search Strategy:

#	Searches	Results
1	exp neoplasm/	3765092
2	exp *carcinoma, squamous cell/	114672
3	(cancer? or malignan$ or premalignan$ or neoplasm? or carcinoma? or dysplasia or tumo?r?).mp.	4735210
4	exp larynx/	42578
5	(laryn$ or (vocal adj2 cord?) or cordal or glotti$ or throat or (voice adj2 box) or subglotti$).mp. or supraglotti$.mp,tw.	154703
6	1 or 2 or 3	5135476
7	4 or 5	158993
8	6 and 7	54357
9	exp radiotherapy/	204346
10	(irradiat$ or radiotherapy$ or radiation).mp,tw.	976577
11	exp surgery/ or dissection/ or endoscopic surgery/ or laser surgery/ or microsurgery/ or excision/	120885
12	(surgery or surgical? or (laryn$ and preserv$) or laryngectom$ or hemilaryngectom$).mp.	3436395
13	9 or 10 or 11 or 12	4246488
14	8 and 13	30773
15	exp comparative study/	1911824
16	14 and 15	2269
17	(case report$ or editorial$ or comment$ or letter$ or news or notes or books).pt.	4389515
18	16 not 17	2207
19	limit 18 to (english language and humans)	1669
20	limit 19 to yr="2011 -Current"	710

Database(s): **Embase** 1996 to 2022 December 01
Search Strategy:

#	Searches	Results
1	exp neoplasm/	4418318
2	exp squamous cell carcinoma/	173769
3	(cancer? or malignan$ or premalignan$ or neoplasm? or carcinoma? or dysplasia or tumo?r or precancer).mp,tw.	5356572
4	exp larynx/	34198
5	(laryn$ or (vocal adj2 cord?) or cordal or glotti$ or throat or (voice adj2 box) or subglotti$).mp. or supraglotti$.mp,tw.	207491
6	exp larynx disorder/	70183
7	1 or 2 or 3	5814853
8	4 or 5 or 6	216682
9	7 and 8	75120
10	exp larynx tumor/	25516
11	9 or 10	75120
12	exp radiotherapy/	554094

13	(irradiat* or radiotherap* or radiation).mp,tw.	1221325
14	exp surgery/ or exp EAR NOSE THROAT SURGERY/ or exp Larynx surgery/ or dissection/ or exp endoscopic surgery/ or exp laser surgery/ or exp microsurgery/ or exp excision/	4783781
15	12 or 13 or 14	5618835
16	11 and 15	45707
17	(case report$ or editorial$ or comment$ or letter$ or news).pt.	1611090
18	16 not 17	44075
19	exp comparative study/	1255704
20	18 and 19	2502
21	limit 20 to (english language and humans)	2268
22	limit 21 to yr="2011 -Current"	1716

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** October 2022**, EBM Reviews - Cochrane Database of Systematic Reviews** 2005 to November 30, 2022
Search Strategy:

#	Searches	Results
1	exp neoplasm/	89393
2	exp squamous cell carcinoma/	3168
3	(cancer: or malignan: or premalignant: or neoplasm: or carcinoma: or dysplasia or tumo?r: or precancer:).mp,tw.	255136
4	exp larynx/	790
5	(larynx: or (vocal adj2 cord:) or cordal or glott: or throat or (voice adj2 box) or subglotti: or supraglotti:).mp,tw.	13141
6	1 or 2 or 3	265010
7	4 or 5	13292
8	6 and 7	2367
9	(irradiat* or radiotherap* or radiation).mp,tw.	57758
10	exp surgery/ or exp EAR NOSE THROAT SURGERY/ or exp Larynx surgery/ or dissection/ or exp endoscopic surgery/ or exp laser surgery/ or exp microsurgery/ or exp excision/	5838
11	exp surgery/ or exp EAR NOSE THROAT SURGERY/ or exp Larynx surgery/ or dissection/ or exp endoscopic surgery/ or exp laser surgery/ or exp microsurgery/ or exp excision/	5838
12	9 or 10 or 11	62299
13	8 and 12	1036
14	(case report$ or editorial$ or comment$ or letter$ or news).pt.	16574
15	13 not 14	1027
16	limit 15 to yr="2011 -Current"	632

DEFINITIONS OF REVIEW OUTCOMES

1. **ARCHIVE** – ARCHIVE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is out of date or has become less relevant. The document will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website and each page is watermarked with the words "ARCHIVE."

2. **ENDORSE** – ENDORSE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is still useful as guidance for clinical decision making. A document may be endorsed because the Expert Panel feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **UPDATE** – UPDATE means the Clinical Expert and/or Expert Panel recognizes that the new evidence pertaining to the guideline topic makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The Expert Panel advises that an update of the document be initiated. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making, unless the recommendations are considered harmful.