Title: **Voice outcomes for early laryngeal cancer**

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**Abstract**

Purpose of review: Treatment options for early laryngeal cancer are well established with good local control and five year survival. The commonest treatments are radiotherapy (RT) or transoral laser microsurgery (TLM). There are advantages and disadvantages of the different modalities but debate continues regarding the voice outcomes post treatment. This review will focus on early glottic carcinoma and voice outcomes following the different treatments.

Recent findings: TLM and RT are both likely to affect voice quality but the extent of voice change depends on different factors. These factors can be divided into patient, tumour and treatment factors. Recent meta-analyses data shows similar voice outcomes for either modality in the treatment of early glottic carcinoma. However larger tumours and those involving the anterior commissure are associated with worse voice outcomes.

Summary: There are various considerations for the patient and clinician before deciding on the preferred treatment for early glottic carcinoma. Although both TLM and RT will affect voice outcomes, the recent meta-analyses show similar voice outcomes for either modality in the treatment of early glottic carcinoma. There are numerous variables in the published studies hindering direct comparisons. These include: heterogeneous patient groups, different treatment standardisation and methods of voice analysis.

Keywords: voice, outcomes, laryngeal, glottic, carcinoma

**Introduction**

Primary radiotherapy (RT) and transoral laser microsurgery (TLM) together with open laryngeal procedures are well established and successful treatments for early laryngeal cancer. High rates of local control and larynx preservation can be achieved with a five year local control rate of 90-93% (for T1a glottic carcinomas) [1,2\*,3]. There are advantages and disadvantages of the different treatment modalities; however all will affect voice outcomes to some degree. In the UK, the use of RT and TLM predominates, with open surgery rarely used. Between, and sometimes within units, there is clinical equipoise, with some units/clinicians preferring RT whilst others predominantly favour TLM [4]. Local decision making typically relates to local expertise, historical precedent and dominant clinical personalities. However, in deciding which is the preferred treatment modality an important aspect is the consideration of the post treatment voice, accepting that in most instances, this relates to perceived outcome rather than objective outcome. There are a number of variables which will affect voice outcomes and these can be divided into patient, tumour and treatment factors. The patient factors include pre-existing co-morbidities and smoking history; tumour factors include stage and site of tumour; treatment factors include the extent of the TLM or RT required for local control of the disease. In this review we will summarise the most recent evidence relating to voice outcomes following treatment for early laryngeal carcinoma.

**Text of review**

Laryngeal carcinoma

Laryngeal cancer accounts for 1% of all new cases of cancer in males and 0.2% in females in the UK [5]. There were 2,315 new laryngeal carcinomas in 2013, 83% of these were in males. Smoking is a major risk factor with alcohol having an additional, synergistic, carcinogenic effect [6]. The larynx is anatomically subdivided into three regions allowing for classification of the tumour site: supraglottis, glottis and subglottis. The glottis includes the true vocal cords as well as the anterior and posterior commissure. According to the AJCC (American Joint Committee on Cancer) the superior boundary of the glottis is a horizontal line through the apex of the laryngeal ventricle whilst the inferior boundary is 1cm below this line [7]. Laryngeal cancers most commonly arise from the glottis and early glottic carcinomas will be the focus of this review. More than 90% of laryngeal cancers are squamous cell carcinomas (SCC) which derive from the epithelium overlying the glottis structures. The majority of patients (up to 75% [8]), present early, with normal vocal cord movement, no cervical lymph node involvement or extension beyond the larynx. As minimal change in the vocal fold mechanics results in voice change, the majority of patients seek attention in a timely manner.

The TNM (tumour, node, and metastasis) classification is used for the staging of laryngeal carcinoma. Early glottic carcinoma includes stages T1a, T1b and T2 with no spread to the cervical lymph nodes (N0) and no distant metastases (M0) see Table 1. Glottic T1a carcinomas are tumours confined to one vocal cord with normal mobility. T1b involves both vocal cords but both cords still move normally. The staging increases to T2 when the tumour extends to the subglottis and/or supraglottis, with or without impairment of vocal cord movement.

Treatment of early laryngeal carcinoma

The aim of treatment is to achieve local control of the disease with preservation of the laryngeal structures in an attempt to maintain optimal voice quality. As stated above, the main treatment options used in the UK are RT or TLM with similar local control rates. The reported five-year-local control is 90-93% in T1a, 85-89% in T1b and 62-97% in T2 glottic carcinomas for either modality [2\*]. There are advantages and disadvantages of both treatments.

RT remains a well established modality in the treatment of early laryngeal cancer. It involves a curative dose delivered in individual fractions over a time period of usually 4-6 weeks. Radical RT may cause acute toxicities including: skin erythema and desquamation, mucositis, dysphagia, long term laryngeal oedema and rarely, oesophageal stricture. There are several treatment regimes but hypofractionation is most frequently used in the UK. The most commonly used fractionation regimens include 50-52.5 Gray (Gy) in 16 fractions over 3 weeks for T1 tumours and 55Gy in 20 fractions over 4 weeks for T1 and T2 disease [9].

In contrast, TLM is usually a day case procedure. However, TLM requires a general anaesthetic, for which some patients may not be fit. Moreover, TLM may not technically be possible in all patients due to poor endoscopic access (e.g. limited extension of cervical spine, prominent incisors and /or relative retrognathia of the mandible or trismus). However, one definite advantage of TLM is that it can be used again in the context of treatment failure providing more options for salvage.

At least with respect to TLM, the extent of the treatment required will vary depending on the site and size of the tumour. Accordingly, in an attempt to standardise surgical nomenclature and facilitate meaningful comparative reporting of outcome data, the European Laryngology Society (ELS) have developed a classification system for larynx TLM which is based on the extent of surgical resection undertaken, see figure 1 [10].

Figure 1: ELS classification of cordectomy (Type I-IV illustrated)



*Source: Remarcle M, Eckel HE, Antonelli A ,et al., European Laryngological Society proposed classification of endoscopic cordectomy (2000). [10]*

Voice outcomes following treatment for glottic carcinoma

TLM and RT are likely to affect voice quality post treatment. Patient, tumour and treatment factors should all be taken into account when recommending treatment options for individual patients.

1. Patient factors

Patients typically present with dysphonia but it is difficult for the clinician to know what is ‘normal’ for them. This problem is exacerbated as there is a wide natural variation in normal voice between genders and with age. For example the fundamental frequency of vocal fold vibration ranges from 60 to 500 Hertz (Hz), with an average of 120Hz in males, 200Hz in females and 270Hz in children [11]. This variation in frequency is determined by the relationship of the length, tension and thickness of the vocal cords, all of which is dependent on individual laryngeal anatomy and physiology as well as patients habitus. For example, more than 75% of patients who present with laryngeal cancer are smokers or have a history of smoking [12, 13]. Smoking, in the absence of cancer, can affect voice in a number of ways and this can be due to multiple aetiologies [14]. Smoking is known to lower the fundamental frequency of voice by inducing an inflammatory infiltrate in the laryngeal mucosa which results in increased oedema of Reinke’s space (Reinke’s oedema)[15]. Smoking also affects voice by reducing lung capacity due to primary pulmonary disease. Other patient factors for consideration include the patients voice use, profession, hobbies, expectations and motivation. Professional voice users will have added anxiety about the impact on their career. However there will be a limited number of professional voice users affected as half of all head and neck cancers are diagnosed in patients over the retirement age (>65years) [5]. For the professional voice user it is important to assess and document their voice pre-treatment as this will be a comparator for the voice post treatment and help guide speech therapy. Speech therapy should be commenced at an early stage in this group of patients to help reduce anxiety and develop a therapy plan.

2. Tumour factors

The primary way early glottic carcinoma interferes with voice quality is by preventing optimal vocal fold apposition and / or negatively impacting on the mucosal waveform. Even small tumours will result in minor mucosal wave perturbation and prevent apposition, whilst tumours which extend more deeply will replace the mucosa and the submucosal space, thereby obliterating a mucosal waveform completely. The extent and depth of tumour will therefore result in a spectrum of worsening dysphonia ranging from a weak voice to roughness. Stroboscopy is required to assess waveform of the vocal fold and a decreased or absent waveform at presentation predicts worse post treatment voice outcomes [16]. The position and size of the tumour will also have an effect on the voice. For example tumours at the anterior commissure can prevent vocal fold contact and cause a breathy voice. These different tumour factors are linked with the different treatments required and the resulting voice outcomes post treatment.

3. Treatment factors

Historically, RT has been thought to have better voice outcomes than laser resection. This is because permanent damage to the vocal fold caused following TLM was assumed to be more significant to that induced by RT. However RT may result in a volume defect and can cause scarring (fibrosis) as a result of local inflammation with a resultant loss or impairment of the mucosal waveform of one or both vocal folds.

A meta-analysis of voice outcomes following treatment of T1a carcinoma was performed in 2015 by Du et al [17\*\*] and included 13 published studies which reported voice outcomes in a total of 125 patients treated with RT and 160 patients treated using TLM. The included studies are methodologically similar (I2=0%, p=0.41). Du et al found no statistically significant difference in one of the most frequently used subjective voice questionnaires, Voice Handicap Index (VHI) scores between patients receiving TLM or RT at a range of between 12 and 60 months (mean difference -2.19, 95% CI -5.75 to 1.37, p=0.23). Greulich et al [18\*\*], in 2015, also performed a systematic review and meta-analysis of voice outcomes following RT or TLM for T1 glottic carcinoma (studies included date from 1997 to 2013). Eight retrospective cohort studies were included (n=362) reporting the voice outcomes of patients treated for T1 glottic carcinoma using VHI scores. This meta-analysis also revealed no significant difference in post treatment VHI scores between RT and TLM groups (mean difference, -5.52; 95% confidence interval, -11.40, 0.36), although the studies were methodologically different (I2 = 61%, p =0.01) and patients were followed up at widely varying post treatment times (mean 47 months, range 1-298months).

It has previously been shown that the extent of the TLM resection is related to loss of contact of the vocal folds causing a glottic gap and resulting in a breathy voice [19]. Accordingly, the type of ELS cordectomy performed may have a direct impact on voice outcome. Vilaseca et al, [20] demonstrated that the more extensive resection of the tumour with TLM the worse the voice outcomes. The extent of the TLM resection varied from type I to V cordectomy in 42 patients treated for T1 glottic carcinoma. The voice was rated by a speech therapist using the GRBAS scale (Grade-Roughness-Breathiness-Asthenia-Strain). The rater was blinded to the type of cordectomy and tumour characteristics. In the 16 patients who underwent extended cordectomy (types IV and V) there was a statistically significantly higher score in all GRBAS domains compared with type I-III cordectomy, with breathiness having the highest mean score across the domains. Roh et al [21] assessed 85 patients treated for T1 glottic carcinoma with TLM. The patients were divided into three groups depending on the extent of the surgery they underwent: type I and II cordectomy (group A), type III or IV cordectomy (group B) and extended or bilateral cordectomy (group C). Video stroboscopic recordings were evaluated pre and post-operatively (median of 20 months, maximum 34 months) by two laryngologists blinded to the extent of treatment. A stroboscopic evaluation form was used which graded each parameter on a scale. The subjective parameters included: vocal fold edge, mucosal wave and glottal closure [22]. Stroboscopic examination revealed larger glottic gaps and reduced mucosal wave in groups B and C.

Mendelsohn et al [19] in 2015 assessed GRBAS scores in 11 patients with T1 (n=5) or T2 (n=6) glottic carcinoma treated with TLM. The authors demonstrated a more breathy voice (as measured by the GRBAS scale) in the period immediately following TLM (up to four months post-operatively) compared with pre-operatively (mean score for ‘B’ 2.50 vs. 0.75 respectively, p=0.003). This longitudinal study also included a second post-operative voice assessment at more than six months post TLM. At the later time point, the data demonstrated that voice quality improved with mean score for ‘B’ decreasing to 1.17. This was a significant improvement from the first post-operative score (mean ‘B’ 1.17 vs. 2.50, p=0.005). They hypothesised that the delayed improvement in breathiness post-TLM was due to the more complete healing of the vocal cord defect, resulting in a smaller glottis gap and improved vocal fold contact.

Tumours involving the anterior commissure (T1b) are associated with poorer local control and voice outcomes [23\*]. The poorer voice outcome is due to the extended resection, in the case of TLM, required, the resultant injury to both vocal folds and the potential for post-surgical complications such as an anterior laryngeal web. A multi-centred study (n=63) compared TLM and RT in the treatment of T1b tumours. The data demonstrated no difference in oncological outcomes or VHI scores between the groups of patients treated using either modality [24]. The local control at two years being 95% for TLM (n=21) and 85.9% for RT (n=42). The post treatment VHI was only available in 23 patients (13 RT, 10 TLM) and the outcomes were recorded up to two years post treatment (0-11 months (median 6 months) for the TLM group and 0-34 months (median 7 months) for the RT group).

Post-treatment fibrosis and stiffening of the vocal cords is associated with an increase in the vocal frequency [25]. It is often assumed that more scarring occurs with TLM compared with RT. However the meta-analysis by Du et al [17\*\*] included three studies, involving a total of 54 patients, treated with RT and 60 patients treated using TLM which measured jitter (an objective acoustic measurement of the waveform-to-waveform perturbation of fundamental frequency (%)) of produced sustained vowels. The included studies were methodologically similar (I2=0%, p=0.80). No statistically significant difference in jitter (%) post-TLM compared with post RT between 21 and 26 months post treatment (mean difference -0.03, 95% CI -0.30 to 0.23, p=0.8) was found.

Voice Rehabilitation

Multidisciplinary Head and Neck Cancer Teams, in the UK (MDT) include speech and language therapists who will see patients before, during and after their treatment. However, the majority of the published literature on voice outcomes in laryngeal carcinoma does not comment on the extent of the voice therapy undertaken for each patient. In a study by Van Gogh et al [26], of 177 patients with early glottic carcinoma only 40% (n=70) suffered from voice impairment at 6-120 months post treatment. This was based on a screening questionnaire consisting of five items including questions regarding vocal ability and voicing in social situations [27]. In this study, 29 patients with pre-treatment voice impairment consented to being randomly assigned to either voice-therapy (n=16) or control (no intervention) (n=13). In the voice therapy group patients attended between 4 and 24 sessions to receive vocal hygiene advice, as well as instruction in breathing and voice exercises. Voice outcomes of patients in the experimental and control groups were measured at least three months post-treatment. The patients who received voice therapy intervention had a significantly better improvement in mean VHI score compared with the control group (15.25 points vs. 2.64 points, p=0.024).

Following laryngeal cancer treatment, most European centres wait at least six months before considering any surgical intervention for voice rehabilitation [28]. This is perceived to allow time for the larynx to heal and voice to recover to a reasonably stable state as well as allowing for the unhindered monitoring of residual or very early recurrent disease.

In cases where there is significant glottic gap following treatment, injection medialisation laryngoplasty can be challenging due to the fibrosis. However, a medialisation thyroplasty with autologous cartilage has been shown to be successful with apparently minimal concerns regarding surveillance for tumour recurrence or interference with revision surgery [29].

Problems with the literature

It is important to understand that there are limitations in the published studies when comparing voice outcomes following treatment for laryngeal carcinoma. Firstly, only one randomised control trial has been attempted comparing the treatment options and voice outcomes for early glottic carcinoma [1]. The UK EaStER (Early Stage Glottic Cancer Endoscopic Excision versus Radiotherapy) trial failed to recruit and closed without reaching the primary endpoint. The main reasons for this was the lack of clinical equipoise and patient preference for day-case TLM rather than a more prolonged course of RT [30]. Other limitations in the literature include the vast array of different methods used to analyse voice outcomes in individual studies: The most common methods include patient reported outcome questionnaires, voice quality perceptual ratings, aerodynamics, acoustic analysis and videolaryngostroboscopy. However the majority of these tools are subjective and have not been validated. The European Laryngological Society (ELS) has produced a protocol in attempt to standardise functional voice outcomes and to allow comparison of the literature [31].

Another common problem is the lack of consistency in the time post-treatment that voice outcomes are captured - a major confounder preventing meaningful comparison between studies. The surgical technique and resection extent also differs widely across reported patient cohorts.

The ELS classification for TLM cordectomy type [10] helps to standardise the extent of resection and significantly aids literature comparison. However the exact extent of cordectomy is difficult to score and is likely subject to wide inter-rater variability although the extent of this variability has not been formally established.

**Conclusion**

TLM and RT are well established modalities for the treatment of early laryngeal cancer with good local control. There are advantages and disadvantages of the different modalities and there are various considerations for the patient and clinician to make before deciding on the preferred treatment. Although both TLM and RT will affect voice outcomes, recent meta-analyses shows similar voice outcomes for either modality in the treatment of early glottic carcinoma, apparently irrespective of how voice quality is recorded.

**Key points**

* Laryngeal carcinoma normally presents early and current established treatments have good local control and five year survival
* Variables which will affect voice outcome can be divided into patient, tumour and treatment factors.
* Recent meta-analyses data demonstrate similar voice outcomes for either TLM or RT in the treatment of early glottic carcinoma.
* Larger tumours and those involving the anterior commissure are associated with worse voice outcomes.

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There are no conflicts of interest to report.

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