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LARYNGOLOGY

CO_2 laser cordectomy for glottic squamous cell carcinoma involving the anterior commissure: voice and oncologic outcomes

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Abstract Transoral CO_2 laser cordectomy for squamous cell carcinoma (SCC) of the glottis has resulted in excellent voice and oncologic outcomes as compared with non-surgical therapy. However, published experience with primary CO_2 laser cordectomy specifically for glottic SCC involving the anterior commissure (AC) is limited. A review of single academic institution experience with CO_2 laser cordectomy for glottic SCC involving the AC. Patients undergoing European Laryngological Society (ELS) classification cordectomy type Va or type VI between 2005 and 2013 were included. Post-surgical voice analysis was performed by speech language pathologists (SLP) from the reporting institution. Thirty patients were identified for inclusion. Mean post-surgical follow-up time was 47.6 months (range 11–59). Initial local recurrence was identified in 5/30 (16.7 %) patients. 2/5 recurrences were successfully salvaged by repeat CO_2 laser resections, 2/5 ultimately required salvage total laryngectomy, and 1/5 patient developed a second primary preventing further curative treatment. Overall laryngeal preservation rate was 28/30 (93.3 %). Overall survival of the study cohort was 96.7 %. Mean postoperative voice handicap index-120 score was 36.9 (SD = 21.4). Perceptual analysis performed on the GRBAS scale resulted in mean scores: $G = 2.1$ (SD = 0.9), $R = 1.3$ (SD = 1.1), $B = 1.6$ (SD = 1.2). Though cancers involving the AC represent an aggressive subgroup of glottic SCC, CO_2 laser cordectomy results in encouraging oncologic and voice outcomes without the need for further therapy in the majority of cases. Clinical trials are encouraged to further define optimal treatment recommendations for glottic SCC involving the AC.

Keywords Larynx · Laryngeal cancer · Vocal cord · Vocal fold · Carcinoma · Cancer · Radiation

Introduction

Despite the controversy that surrounds the treatment of glottic squamous cell carcinoma (SCC) involving the anterior commissure (AC), one factor has been consistently demonstrated: AC involvement is a negative prognostic indicator for both oncologic and voice outcomes, regardless of treatment modality. While the pathophysiologic basis for the increased aggressiveness of this laryngeal cancer subsite requires further study, the published clinical experience regarding the treatment outcomes for SCC involving the AC is limited. In particular, the published endoscopic CO_2 laser cordectomy experience to date has typically reported either oncologic outcomes [1–3] or voice outcomes with quality of life descriptions [4]. However, when evaluating the treatment recommendations for AC carcinomas consideration of both oncologic and voice outcomes is required and little is currently known regarding the oncologic and voice outcomes within a single patient cohort [5]. The authors therefore set out to describe the combine outcomes from a single academic institution with CO_2 laser cordectomy treating SCC of the AC.

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Methods

Institutional review board (IRB) approval was obtained for the research methods described.

Within the present academic medical center, patients with SCC of the glottis are offered either CO_2 laser cordectomy or primary radiotherapy. Based on comparative excellent oncologic outcomes, voice outcomes, length of treatment, and cost of treatment, the authors consider transoral laser microsurgery the primary treatment recommendation for patients with glottic SCC unless otherwise contraindicated. Contraindications for endoscopic surgical resection include: vocal process fixation, preoperative evidence of thyroid/cricoid cartilage invasion, medical comorbidities precluding general anesthesia, and anatomic limitations resulting in poor endoscopic exposure. Those patients who decide on surgical therapy are taken to the operating room where CO_2 laser cordectomy is performed as previously described by the European Laryngological Society (ELS) [6, 7]. Briefly, the ELS cordectomy classification includes: type I (subepithelial), type II (subligamental), type III (intramuscular), type IV (complete cordectomy), type V (advanced cordectomy), type Va (unilateral cordectomy with continuation onto the contralateral fold with resection of anterior commissure), type VI (anterior commissure resection). Patients with SCC with visible tumor encroaching to the anterior-most extent of a single membranous vocal fold or SCC extending continuously from one membranous fold to the other are defined as AC-involved glottic SCC. These patients undergo either ELS cordectomy type Va or type VI as determined by the operative surgeon. Examples of pre- and post-operative laryngoscopy for cordectomy types Va and VI are demonstrated in Fig. 1.

Postoperatively, patients are observed for a minimum of 3 h with many patients undergoing extended cordectomy are observed overnight in the hospital before discharge home. Patients are recommended to practice 7–10 days of strict voice rest. Patients are treated with anti-reflux medication. Out-patient clinical examinations with indirect laryngoscopy are scheduled for 2 and 4 weeks postoperatively, then on a bimonthly basis. Patients are referred for voice therapy with experienced SLP following the first clinical follow-up examination.

At a time point of 4–6 months postoperatively, patients undergo formal objective and perceptual voice assessment by the treating speech language pathology (SLP) team. At the time of the post-treatment voice evaluations, patients are routinely asked to complete the full 120 question version of the voice handicap index (VHI) [8] as the patient-reported outcome measure.

As part of the objective laryngeal evaluation, maximum phonation time (MPT) and pulmonary vital capacity (VC) are recorded. From these measures, phonation quotient (PQ) is calculated by dividing vital capacity by MPT for a result measured in cc/s. Perceptual grading is performed by the SLP and is scored according to the established GRBAS classification system [9]. Select patients who demonstrate subjective and objective evidence of dysphonia are considered for medialization procedures (injection laryngoplasty or type I thyroplasty) only following a span of 6 months postoperatively.

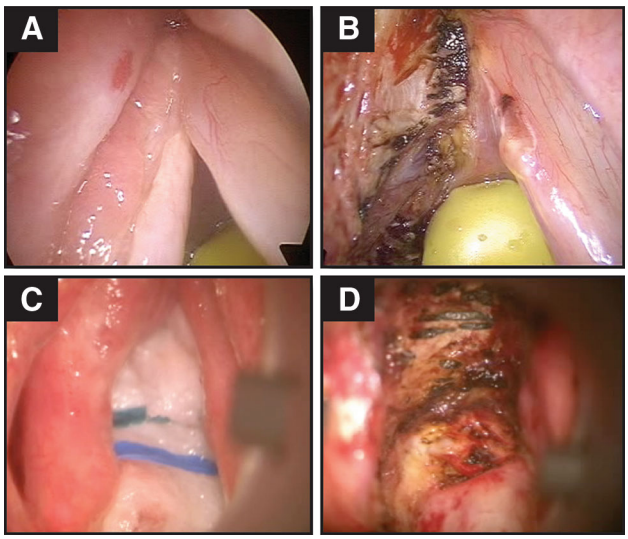

Fig. 1 Pre- and post-operative laryngoscopy following CO_2 laser cordectomy. **a** Displays a glottic carcinoma arising from the superior surface of the membranous vocal fold, extending from the vocal process to the anterior commissure. As displayed in **b**, an ELS type Va CO_2 laser cordectomy was performed in this case resecting the entire left vocal fold, the left false fold, and the anterior commissure (note the carbonization marks anteriorly signifying purposeful entry into the inner aspect of the thyroid cartilage). **c** Demonstrates an invasive carcinoma of the left mid-membranous vocal fold extending into the anterior commissure (note the altered appearance of bilateral vocal folds typical of recent ELS type I diagnostic cordectomies). An ELS type VI cordectomy was performed in this case as demonstrated in (**d**) (again note the intentional anterior carbonization marks into the thyroid cartilage)

Patients who received CO_2 laser cordectomy for glottic SCC at the reporting institution were prospectively collected in a surgical database. This database was searched between the dates of March 2005 and March 2013 for patients who received advanced ELS CO_2 laser cordectomy type Va or VI. Pathology reports were reviewed to include only patients with the histopathologic diagnosis of squamous cell carcinoma. Medical history was reviewed to exclude patients with a history of prior treatment for glottic cancer (either failed radiotherapy or surgical excision). Of note, patients with limited (ELS type I) laser cordectomy as part of their diagnostic pathway, as previously described [6], were included in the study. No patient in the present study underwent elective surgical management of regional

Table 1 Oncologic outcomes following CO_2 laser cordectomy for glottic SCC involving the anterior commissure by tumor stage

	T_{1a} ($n = 11$)	T_{1b} ($n = 10$)	T_2 ($n = 9$)	Overall ($n = 30$)
Gender				
Female	1	1	0	2
Male	10	9	9	28
Age at surgery [mean years (SD)]	61.1 (7.8)	60.5 (11.8)	64.6 (12.9)	61.9 (10.7)
Local recurrence	3 (27.3 %)	2 (20.0 %)	0 (0 %)	5 (16.7 %)
Progression to total laryngectomy	1 (9.1 %)	1 (10.0 %)	0 (0 %)	2 (6.7 %)

SCC squamous cell carcinoma, *SD* standard deviation

lymphatics. Those patients who required further vocal augmentation procedures had their voice assessments recorded from their pre-augmentation levels. The effects of post-cordectomy augmentation are the focus of separate study.

Univariate associations were identified through non-parametric statistical analysis. p values of ≤ 0.05 were deemed significant. Statistical analysis was performed using Stata Statistics/Data Analysis v. 12.0 (College Station, TX, USA).

Results

Thirty patients received CO_2 laser cordectomy as primary treatment for glottic squamous cell carcinoma (SCC) involving the anterior commissure (AC) and were included in this analysis. Clinical follow-up time was an average 47.6 months (range 11–59 months). Oncologic outcomes are displayed in Table 1 stratified by T-stage. Risk of local recurrence was not significantly associated with age, gender, tumor stage, or type of cordectomy ($p > 0.05$).

There were five tumor recurrences seen within AC-involved SCC patients, all of which were local recurrences. The average time to recurrence was 20.6 months (range 12–26 months). Of the five recurrences, one patient demonstrated a local recurrence that required prompt salvage total laryngectomy. The patient's presentation with local recurrence extending beyond the external thyroid cartilage border precluded the recommendation for upfront external beam radiation. One other patient's recurrence presented simultaneously with a large second primary cancer and was deemed a candidate for palliative care only due to the incurative nature of that second primary. Three of the five local recurrences were returned to the operating room for transoral CO_2 laser re-resection. Two of these re-treated patients were successfully salvaged, while the remaining patient had persistent positive intraoperative margins necessitating total laryngectomy. Again, the gross invasion of the thyroid cartilage precluded recommendation for salvage external beam radiotherapy.

Overall, laryngeal preservation following ELS cordectomy for SCC involving the AC was 93.3 %. Overall local tumor relapse rate was 16.7 %, leading to an initial disease-free survival of 83.3 %. Ultimate disease-free survival following salvage surgery was 96.7 %. Overall survival of the study cohort was 96.7 %.

Voice outcomes following CO_2 laser cordectomy involving the AC are presented in Table 2, stratified by T-stage. Only the request for voice augmentation procedures (injection laryngoplasty or medialization thyroplasty) was significantly associated with increased primary T-stage (Chi-square $p = 0.05$). However, with the overall small number of patients requiring augmentation, this result should be interpreted with caution. Of the four patients who required voice augmentation with medialization thyroplasty, the average time to post-operative procedure was 20.0 months (range 9–30 months). One patient required injection laryngoplasty and this was performed 6 months post-operatively.

Discussion

Controversy has surrounded treatment recommendations for glottic squamous cell carcinoma (SCC) with involvement of the anterior commissure (AC). The debate has focused on discerning which treatment choice can be offered to counterbalance the poorer outcomes of AC involved tumors as compared with similar staged glottic tumors without AC involvement. In the published literature, there have been proposed mechanisms to explain the oncologic aggressiveness of the AC: anatomic, biologic, or therapeutic shortcomings.

The chief anatomic concern historically was concerned with defining the role of the anterior commissure ligament, otherwise known as Broyles' ligament [10], in the pattern of SCC spread. Broyles' ligament is formed through the continuation of the vocal ligament fibers as they course to the anterior-most portion of the membranous vocal fold and attach deep to the inner perichondrial layer of the thyroid cartilage. The anatomic debate centered on whether these fibers served as a route of tumor spread or served as a

Table 2 Voice outcomes following CO_2 laser cordectomy for glottic SCC involving the anterior commissure by tumor stage

	T_{1a} ($n = 11$)	T_{1b} ($n = 10$)	T_2 ($n = 9$)	Overall ($n = 30$)
Gender				
Female	1	1	0	2
Male	10	9	9	28
Age at surgery [mean years (SD)]	61.1 (7.8)	60.5 (11.8)	64.6 (12.9)	61.9 (10.7)
Injection laryngoplasty or medialization thyroplasty	1 (9.1 %)	5 (50 %)*	1 (11.1 %)	7 (23.3 %)
VHI [mean score (SD)]	38.4 (9.4)	36.9 (28.3)	33.5 (7.8)	36.9 (21.4)
Maximum phonation time [mean seconds (SD)]	2.6 (2.3)	10.5 (5.7)	3.2 (1.1)	7.4 (5.8)
Phonation quotient [mean cc/s (SD)]	569 (148)	430 (279)	679 (287)	515 (268)
Perceptual rating score [mean score (SD)]				
G	2.5 (0.6)	1.6 (0.9)	2.7 (0.6)	2.1 (0.9)
R	1.8 (1.3)	0.8 (0.7)	1.7 (1.5)	1.3 (1.1)
B	2.0 (0.8)	1.1 (1.2)	2.1 (1.7)	1.6 (1.2)
A	0	0	0	0
S	1.8 (1.5)	1.1 (0.9)	1.3 (1.2)	1.4 (1.1)

SCC squamous cell carcinoma, *SD* standard deviation, *VHI* voice handicap index, *G* grade, *R* roughness, *B* breathiness, *A* asthenia, *S* strain

* Chi square $p = 0.05$

barrier to invasion. Following dedicated study of laryngeal cancer growth patterns [11] it is now generally accepted that Broyles' ligament is protective against direct tumor invasion to the cartilage, as the ligament confines carcinomas within the soft tissue of the glottis. However, this protective barrier is not absolute and AC cartilage invasion is at risk particularly when supraglottic or subglottic extent is identified along the course of the carcinoma's tract within the AC [11].

It may also be suggested that AC-involved tumors tend to be biologically more aggressive. It is known that the most common site for glottic carcinogenesis is the membranous vocal fold between the mid-point and the anterior third of the fold. Tumors that arises de novo from the AC, or show AC involvement by anterior tumor extension may arise from a more widespread oncologic mutational change suggesting a higher risk of local recurrence from subclinically involved peripheral margins. On an intracellular level, it has been suggested that significant differences in epidermal growth factor receptor (EGFR) expression is related to the anatomic position of glottic tumor growth [12], which underscores the concern of increased biologic aggressiveness of AC tumors. In either method of explanation, the involvement of the AC may de facto result from a biologically more aggressive carcinoma.

Debate has also centered on therapeutic effectiveness for this aggressive subsite of the glottis. Regarding external beam radiation therapy, historically the ability to fully treat the AC was questioned. Early reports with external beam radiation therapy demonstrated poor oncologic control, specifically when the energy was delivered in Megavoltage radiotherapy technique compared with Cobalt-60, as this technique better delivered energy to structures close to the air-tissue interface [13]. However, even with the improved energy delivery techniques of the past few decades, AC involvement is routinely seen as an independent negative prognostic indicator across treatment studies.

Also from a therapeutic standpoint, the recommended surgical approach has also been debated for AC-involved SCC. Though endoscopic approaches to laryngeal cancer, has been practiced for well over 40 years [14], many still argue that only an open approach may achieve full tumor clearance of the anterior commissure. While some may go so far as to recommend total laryngectomy, most who support the recommendation for open surgery will offer some variation of Tucker's frontolateral partial laryngectomy [15]. However, these surgical approaches have not been shown to be demonstrably superior from an oncologic standpoint from the endoscopic alternative, which the open approaches do suffer from significant functional limitations.

The endoscopic approach to AC-involved SCC is supported by one of the largest single site series of endoscopic resection of AC cancer from Steiner and colleagues experience with CO_2 laser cordectomies [3]. Describing outcomes from 153 glottic SCC with AC-involvement. Steiner's cohort were similarly confined to T_1 and T_2 cancers, where 62 of the 152 patients developed initial local recurrences. This experience results in an initial local recurrence rate of 40.5 %, though their ultimate local recurrence rate was improved by staged repeated CO_2 laser resections. Our described experience then compares favorably with the Steiner experience demonstrating a 16.7 % initial rate of local recurrence and a much

improved ultimate local control rate following salvage resections. Additionally, the Göttingen experience did identify small numbers of regional recurrences which was not seen in the present report. The inconsistency for recurrence patterns may be explained through the increased patient count, and study power, of Steiner and colleagues (153 vs. 30). The concern for regional recurrence following treatment of AC-involved SCC requires further investigations across reporting institutions. Interestingly the oncologic data here demonstrated a local recurrence rate trend suggesting that T_1 tumors with AC involvement may result in poorer oncologic outcomes than T_2 tumors with AC involvement. Though this trend was not confirmed on statistical analysis, similar possible trends have been seen elsewhere, in particular within the Göttingen experience [3]. This contrary local recurrence trend may represent limitations in the current clinical staging systems to account for the local aggressiveness of glottic SCC.

Additional studies evaluating endoscopic cordectomy of have reported similar oncologic success rates comparative with the present study [1, 2]. Although oncologic outcomes are poorer in SCC with AC-involvement as compared with SCC without AC-involvement, CO_2 laser cordectomy continues to demonstrate excellent local control and laryngeal preservation rates as compared with the other therapeutic options of radiation therapy [16] and open surgery [15, 17].

A comparative review of published voice outcomes following AC resection is challenging as dedicated voice analysis following surgical treatment specifically of the AC has rarely been reported. However, we are able to find that long-term post-surgical GRBAS scores within the 1.0–1.5 range (scores 1–2 imply mild to moderate impairment) as reported presently, is consistent with voice outcomes following early glottic cancer surgery for both AC and non-AC tumors [4, 18]. While an effect on the voice is clearly seen, the overall magnitude is mild and can be interpreted as successful voice preservation approach.

The patient-reported outcome measure used in the present study was the 120-question VHI. The number of CO_2 laser cordectomy publications reporting post-operative outcomes following AC resection with VHI is limited. However, our patient cohort average post-operative score of 36.9 compared favorably with the moderate voice impact as reported by Taylor et al. [5] treating only T_{1b} glottic tumors. Our post-surgical patients admittedly demonstrate some level of handicap of the vocal function, yet with an overall mean score 36.9 overall acceptable patient-perceived vocal function is seen. AC-involved SCC has also been associated with poorer voice outcomes following primary radiation therapy. When compared with similarly staged glottic tumors without AC involvement, AC-involved SCC following primary radiotherapy resulted in significantly increased minimum voice intensity, which is thought as a marker for elevated vocal effort and laryngeal dysfunction [19].

Objective glottic functional measurements were also described in our treatment cohort. The MPT was far below normal levels with average MPT of 7.4 s. Post-surgical PQ averaged 515 cc/s. A PQ within this level does show comparison to glottic functioning with benign laryngeal pathology yet the PQ magnitude demonstrated in our patient cohort is comparatively minimal when comparing to the PQ of glottic incompetency states such as vocal fold paralysis [20].

In discussing this study, there are a number of shortcomings that must be reviewed. First, the absence of pre-operative vocal analysis precludes an inclusion of a matched control group. The importance of this shortcoming should be reiterated. To comprehensively evaluate the vocal effects of any treatment for glottal cancer, both pre- and post-treatment voice analysis must be carried out. One of the main goals of the present analysis was to underscore the importance of voice analysis in future publications of glottic cancer treatment and from this perspective this study is successful. The ultimate conclusions that may be drawn from such a descriptive study must be tempered and additional study must be carried out. Additionally, the overall study population is somewhat limited in size and the study power is likewise limited. However, the purpose of this study was not to definitively identify the optimal treatment modality for AC cancers; rather, the authors set out to combine oncologic and voice outcomes in single study as has not been performed routinely. In this goal though, the cohort of AC-involved SCC is heterogeneous in regards to tumor stage. Though consideration was given to limiting the study cohort to a specific T-stage, ultimately the overall patient numbers precluded this level of sub-categorization. Last, critical analysis of this study can identify the absence of synechiae description. Laser surgery of the AC carries a risk of synechiae formation bridging the membranous vocal folds. However, without an acceptable staging or classification scheme for synechiae, little beyond descriptive terms (mild, moderate, severe) could be utilized. The authors therefore subsumed synechiae formation outcomes into the functional voice outcomes, noting mainly that clinically significant synechiae formation is observable within the perceptual and objective voice measures.

The goal of the present study was to describe within a single patient cohort the combined voice and oncologic outcomes following glottic SCC. The authors wish to underscore the importance of including both aspects of patient outcome analysis in future studies of AC-involved glottic SCC. The data presented here is designed to be incorporated into future meta-analysis as well as in

planning future randomized clinical trials comparing available treatment modalities for this challenging anatomic site.

In conclusion, glottic SCC involving the AC is known to be an aggressive subgroup of laryngeal cancer. Regardless of treatment choices, tumors involving the AC can be expected to demonstrate poorer oncologic and functional outcomes. While no single modality has been identified as the optimal choice, CO_2 laser cordectomy can achieve excellent oncologic outcomes, vocal function, and rates of organ preservation. Additional clinical trials are required for the identification of definitive treatment recommendations for glottic carcinoma involving the AC.

Conflict of interest Dr. Mendelsohn is a paid consultant for Lumenis Inc.

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