Vocal Outcomes After Laser Resection of Early-Stage Glottic Cancer With Adjuvant Cryotherapy

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Objective: To evaluate the vocal outcomes of patients with early-stage glottic carcinoma undergoing laser resection with adjuvant cryoablative therapy.

Design: Retrospective review.

Setting: Tertiary care center.

Patients: Twenty patients with early-stage glottic carcinoma.

Intervention: Treatment of early-stage glottic carcinoma with endoscopic carbon dioxide laser resection in conjunction with cryoablative therapy.

Main Outcome Measures: Disease-free survival and subjective and objective measures of posttreatment voice quality, based on serial videolaryngostroboscopy.

Results: There was 1 local treatment failure, with an overall mean disease-free follow-up of 32.6 months (range, 3-93 months). Carbon dioxide laser resection and cryoablative therapy were associated with a significant improvement in subjective voice quality ($P < .001$). Long-term dysphonia was uniformly improved vis-à-vis the pretreatment condition, even among patients with the most advanced disease undergoing the widest resections. Posttreatment web formation was not noted among 4 patients with anterior commissure involvement.

Conclusions: Endoscopic laser laryngeal surgery performed in conjunction with cryotherapy for early-stage glottic carcinoma yielded excellent primary site control, while improving subjective and objective measures of voice quality. Combined laser surgery and cryotherapy is a possible alternative to radiotherapy for selected patients with early-stage glottic carcinoma who desire curative therapy, while optimizing vocal outcomes.

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The treatment of early-stage glottic carcinoma has evolved over the past several decades. External beam radiotherapy is the standard treatment, which usually maintains laryngeal form and function, has a high rate of locoregional treatment success, and indirectly treats other regional premalignant mucosal lesions. However, significant morbidity is associated with this treatment modality, with complication rates ranging from 10% to 45%.

Nevertheless, this organ-sparing approach is commonly associated with excellent posttreatment voice quality. Laser surgery, another treatment option, avoids many of these morbidities. It limits treatment to the tissues undergoing malignant change, avoids the morbidity of radiation transit through the neck, is cost-effective, and affords excellent tumor surveillance. In addition, laser therapy offers long-term oncologic control and vocal results that are almost equivalent to those associated with external beam radiation. However, a recent study concluded that postendoscopic surgery voice quality is poor when the plane of dissection disrupts the vocal ligament and includes part or all of the vocalis muscle.

Excellent long-term posttreatment vocal outcomes were anecdotally noted in a cohort of patients with early-stage glottic carcinoma undergoing combined laser surgery with adjuvant cryotherapy at the Head and Neck Institute, The Cleveland Clinic Foundation, Cleveland, Ohio. Therefore, the present study was undertaken to evaluate the vocal outcomes of patients undergoing this combined treatment. Oncologic outcomes were also investigated to assess the potential for the addition of cryotherapy to aid in the long-term control of primary or recurrent glottic carcinoma.
METHODS

A retrospective medical record review identified 20 patients with biopsy-proven primary or recurrent glottic squamous cell carcinoma who underwent treatment with combined endoscopic laser surgery and cryoablation from April 1, 1997, to April 1, 2004, at the Head and Neck Institute. One of us (M.S.) treated all 20 patients using a carbon dioxide laser with 5 W of continuous or superpulsed energy in a narrow-beam configuration. Cryotherapy was provided with a laryngeal probe (Frigitronics; CooperSurgical, Inc, Trumbull, Conn) to a maximum temperature of −40°C in 3-mm overlapping applications covering the entire tumor bed. Frozen-section margin analysis was performed on all patients before initiating cryotherapy. No patients were brought back to the operating room for close or positive margins on permanent-section analysis.

We recorded the following patient data: sex, tumor stage and grade, extent of the resection, postoperative complications, rate of locoregional recurrence and distant metastasis, and duration of postoperative follow-up. We also made special note of patients who had received pretreatment with external beam radiotherapy and patients whose glottic cancer involved the anterior commissure. The extent of the resection was graded according to the criteria of the European Laryngological Society Working Committee (ELSWC) (Table 1). Disease-free survival was assessed based on scheduled follow-up examinations, including fiberoptic laryngoscopy and videostroboscopy and biannual chest radiographs.

Before undergoing surgical treatment, all patients’ conditions were comprehensively evaluated and the results were presented at a multidisciplinary tumor board that included head and neck surgeons, a radiation oncologist, and a medical oncologist. Patients were informed of the risks and benefits of combined endoscopic laser laryngeal surgery and cryotherapy and were informed of treatment alternatives.

At data collection, patients were contacted by a third party and were asked to retrospectively analyze their preoperative and postoperative voice quality using a 10-point scale, with 1 representing the poorest possible voice and 10 representing the best possible voice. Patients were also asked to compare their current voice quality with their preoperative condition using a 100-point dysphonia scale, with 100 representing the worst possible vocal outcome and 1 representing a normal voice. Descriptive statistics were recorded and analyzed comparing the mean dysphonia with the extent of resection, tumor grade, involvement of the anterior commissure, and prior exposure to radiotherapy.

RESULTS

Tokyo, Japan) and Kay (Pentax Medical Company, Montvale, NJ) digital machines were used to record data. Three blinded voice professionals (C.F.M., D.M.H., and T.I.A.) evaluated each videostroboscopic encounter. Because most of the patients had multiple videostroboscopic recordings, the encounters were divided into 3 temporal categories: preoperative assessment, first postoperative assessment (1-2 months after surgery), and final postoperative assessment (3-93 months after surgery). Although the professionals were blinded to the patients’ identities and treatment course, the randomized videostroboscopic encounters for each patient were reviewed as a collection to minimize interpatient variability. Reviewers assessed each encounter according to a 100-point dysphonia scale, with 100 representing the worst possible vocal outcome and 1 representing a normal voice. Descriptive statistics were recorded and analyzed comparing the mean dysphonia with the extent of resection, tumor grade, involvement of the anterior commissure, and prior exposure to radiotherapy.

Table 2 gives the patient data and tumor grade and histologic findings. The overall mean disease-free follow-up was 32.6 months (range, 3-93 months). There was 1 local treatment failure, which was salvaged by a revision endoscopic laser cordectomy with cryoablation; this patient is disease free. A second patient who had chosen not to continue returned to the clinic with a second primary glottic mass with lung metastases more than 7 years following successful combined treatment for a poorly differentiated T1b tumor. Three of 20 patients had undergone external beam radiotherapy with curative intent at outside institutions before enrollment in the present study.

The median ± SD self-reported preoperative voice quality was 4.00 ± 1.94 on a 10-point scale, whereas the self-reported postoperative voice quality was 8.00 ± 2.42 on a 10-point scale. Of 20 patients, 17 (85%) described their voices as somewhat or much improved, while only 1 patient described his voice as somewhat worse following combined laser surgery and cryotherapy. Carbon diox-

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<th>Table 1. Classification of Endoscopic Cordectomies Proposed by the European Laryngological Society Working Committee</th>
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<td><strong>Type of Cordectomy</strong></td>
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<td>1 Subepithelial</td>
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<td>2 Subligamental</td>
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<td>3 Transmuscular</td>
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<td>4 Total</td>
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<th>Table 2. Patient Characteristics, Histopathologic Classification, and Tumor Grade*</th>
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<td><strong>Variable</strong></td>
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<td>---------------------------------</td>
</tr>
<tr>
<td>Underwent previous radiotherapy</td>
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<td>Involvement of anterior commissure</td>
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<td>Tumor grade</td>
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<td>Carcinoma in situ</td>
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<td>T1a</td>
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<td>T2</td>
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<td>Histopathologic classification</td>
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<tr>
<td>Invasive</td>
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<td>Well differentiated</td>
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<td>Spindle cell variant</td>
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*All patients were male. The mean (median) follow-up was 32.6 (26.7) months.
ide laser resection and cryoablative therapy were associated with a significant improvement in subjective voice quality (P<.001).

A comparison of pretreatment dysphonia with early postoperative and long-term posttreatment dysphonia was performed according to the ELSWC criteria (Figure 1). Compared with the pretreatment condition, patients undergoing a type 1 resection, which is limited to the superficial layer of the lamina propria, experienced a mean improvement in voice quality of 12.8% (pretreatment mean dysphonia score of 39 vs posttreatment mean dysphonia score of 34) in the early postoperative period, which was followed by a 46.2% (pretreatment score of 39 vs posttreatment score of 21) mean improvement in the long term. The mean dysphonia among patients undergoing a type 2 resection, which is limited to the superficial aspect of the vocalis muscle, demonstrated an initial improvement of 10.3% (32 vs 29) in the early postoperative period, increasing to 44.8% (29 vs 16) in the final evaluation. When the resection included the medial portion of the vocalis muscle (ELSWC type 3), the initial voice quality was essentially unchanged (43 vs 42) but demonstrated a long-term improvement of 30.3% (43 vs 30). When the surgical resection included the inner perichondrium of the thyroid lamina (ELSWC type 4), the mean early dysphonia demonstrated a marginal deterioration of 2.7% (72 vs 74), but in the long term the dysphonia improved by 55.6% (72 vs 32).

An analysis of voice quality by tumor stage (carcinoma in situ, T1a, T1b, and T2) was also performed (Figure 2). Patients with carcinoma in situ experienced a minimal improvement of 7.5% (pretreatment mean dysphonia score of 36 vs posttreatment mean dysphonia score of 33.3) in the immediate postoperative period. The mean dysphonia in this group improved by 39.8% (36 vs 21.6) in the long term. Among patients with stage T1a malignancies, the mean dysphonia initially improved by 18.7% (40.7 vs 33.1), with patients experiencing a 53% (40.7 vs 19.1) improvement by the final evaluation. Patients with stage T1b glottic carcinoma experienced a deterioration in their mean dysphonia score of 12.1% (33 vs 37) during the early postoperative period, while over the long term these patients experienced an improvement of 42.4% (33 vs 19). The mean dysphonia among patients with stage T2 disease demonstrated an initial 61.1% (36 vs 58) deterioration, but voice quality improved by 13.9% (36 vs 31) in the long term.

When the anterior commissure was involved in the tumor resection, early voice quality was essentially unchanged (pretreatment mean dysphonia score of 51 vs posttreatment mean dysphonia score of 50), but in the long term the mean dysphonia scores among these patients improved by 43.2% (51 vs 29). No patients with anterior commissure involvement were noted to develop posttreatment anterior glottic webs. Among 3 patients whose disease failed to respond to initial treatment with radiotherapy, the early mean dysphonia was unchanged compared with pretreatment values (33 vs 33), but the mean dysphonia improved by 30.3% (33 vs 23) over the long term.

**COMMENT**

Vocal outcomes following treatment of early-stage glottic carcinoma have been well studied. Although endoscopic surgery has been established as an oncologically sound treatment alternative compared with external beam radiotherapy, the data regarding speech quality offered by these organ-preserving strategies are mixed. Scarring and tissue fibrosis adjacent to the laser ablation crater have been attributed to decreased mucosal wave formation. Nevertheless, the development of newer generations of lasers with lower power settings, narrower beam sizes, and superpulse features allowing for greater thermal relaxation time have limited this damage. Despite these improvements, endoscopic laser therapy has not been found to offer significant improvement in posttreatment voice quality. Although 1 study demonstrated improvements in such measures as jitter, shimmer, fundamental frequency, and mean phonation time compared with control groups undergoing radiotherapy, other studies have demonstrated equivalent outcomes or worse speech outcomes compared with radiotherapy. Although a true meta-analysis is lacking, it seems as if endoscopic laser surgery is, at best, associated with speech outcomes.
that are marginally worse than the vocal results associated with external beam radiation.

One of us (M.S.) introduced cryotherapy as adjuvant treatment in patients undergoing laser resections of early glottic cancer with the assumption that the addition of cryotherapy would fundamentally alter the remodeling phase of wound healing. By causing local vascular infarction, cryotherapy may reduce the influx of inflammatory cells into the ablation crater. Furthermore, the necrotic postcryoablated tissue may act as a biologic membrane over the resection margin, potentially enhancing tissue healing. This effect may explain the lack of anterior glottic web formation in any of our patients, even in those with anterior commissure involvement.

In this study, the use of combined laser laryngeal surgery and endoscopic cryotherapy seems to be associated with improvements in subjective voice quality. Other studies have used subjective measures of voice quality and reported positive and negative results. Nevertheless, among this cohort of 20 patients, a low P value was obtained (P < .001), indicating that this effect is unlikely to be due to random chance.

Most important, vocal outcomes were objectively evaluated by 3 blinded voice professionals using the dysphonia index. This 100-point continuous data scale is the most clinically relevant outcome measure for postoperative voice quality. Irrespective of the extent of tumor resection, patients in our study experienced long-term improvement in dysphonia, with the patients undergoing ELSWC type 1 and 2 resections experiencing final voice quality within 20% of normal (Figure 1). Even patients undergoing resections that included the entire vocalis muscle (ELSWC type 3) and the perichondrium of the inner thyroid lamina (ELSWC type 4) had long-term improvements in voice quality, with final voice quality within approximately 30% of normal. Similar results were obtained when vocal outcomes were analyzed according to tumor stage. T2 tumors were associated with an early deterioration in voice quality, followed by substantial improvements in voice quality over the long term. Several patients undergoing ELSWC type 3 resections demonstrated a return of mucosal pliability and wave propagation. These results differ from those of previous techniques in which voice quality deteriorates when the depth of the resection margin includes the vocalis muscle.

We also analyzed the vocal outcomes among the patients who failed initial radiotherapy and among the patients whose tumors involved the anterior commissure. Our results agree with previous findings that these patient groups experience substantial long-term improvements in their mean dysphonia.24

Cryotherapy is a well-studied technology that has been used routinely to treat various benign tumors of the skin and to control various malignant processes. Although cryotherapy has been used for several decades, its use in human glottic carcinoma has not been thoroughly investigated.25,26 Initial enthusiasm with its use as monotherapy in the 1970s waned because of technical flaws and unacceptable rates of recurrence. When used as adjuvant therapy, cryosurgery theoretically provides additional margin control. Tissue necrosis is achieved when the temperature is rapidly reduced below −30°C, causing intracellular crystallization of water, denaturation of proteins, and accumulation of toxic electrolyte concentrations.27 These changes cause local cellular necrosis, while preferentially permitting some of the extracellular matrix protein to survive.

The combined use of cryosurgery and endoscopic laser laryngeal surgery can potentially improve oncologic outcomes without compromising postoperative voice quality. Precise intraoperative margin control may be difficult to achieve with the use of frozen-section analysis of laser-ablated tissue. Thermal damage to the tissue samples and coarctation of the specimen edge during specimen preparation may lead to false-negative results on histopathologic evaluation. The use of adjuvant cryosurgery offers several millimeters of tissue necrosis when used in an overlapping fashion. This additional margin may represent an important benefit when considering complete tumor eradication in the complex 3-dimensional anatomy of the human larynx. Only 1 patient in our study experienced recurrent glottic carcinoma during follow-up. Salvage treatment, which consisted of a second combined endoscopic procedure, was successful. Furthermore, an additional 2 patients had close margins on permanent-section analysis, but they have not developed recurrences on laryngovideostroboscopic and subsequent intraoperative suspension microlaryngeal follow-up. Therefore, the use of cryotherapy may prevent a return to the operating room for additional resections for patients with close margins on permanent sections, which is commonly documented in the endoscopic laryngeal cancer literature.

Our study has several limitations. The lack of a control group prevented us from comparing outcomes between combined endoscopic laser and cryosurgery with those of a more accepted treatment modality. As with any retrospective analysis, the patients' assessment of pretreatment and posttreatment voice quality is subject to recall bias. Furthermore, the limited number of patients restricted our analysis to descriptive statistics. Nevertheless, the surprisingly good vocal results obtained using combined therapy warranted a preliminary investigation.

**CONCLUSIONS**

Endoscopic laser laryngeal surgery performed in conjunction with cryotherapy of early-stage glottic carcinoma yielded excellent primary site and locoregional control while significantly improving subjective voice quality. Analysis of videostroboscopy data demonstrated that, although deeper resection margins were associated with worse vocal outcomes, ELSWC type 3 and type 4 resections were associated with substantial improvements in voice quality compared with the pretreatment condition. We believe that combined laser surgery and cryotherapy is a possible alternative to radiotherapy for selected patients with early-stage glottic carcinoma who desire curative therapy, with improved vocal outcomes. Based on our preliminary results, the process of glottic wound healing and tissue remodeling following laser surgery and cryoablative procedures should be thoroughly investigated.
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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Knott, Milstein, and Strome. Acquisition of data: Knott, Milstein, Hicks, and Byrd. Analysis and interpretation of data: Knott, Milstein, Hicks, Abelson, and Strome. Drafting of the manuscript: Knott and Strome. Critical revision of the manuscript for important intellectual content: Knott, Milstein, Hicks, Abelson, Byrd, and Strome. Statistical analysis: Hicks. Obtained funding: Knott. Administrative, technical, and material support: Milstein, Hicks, and Byrd. Study supervision: Knott and Strome.

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REFERENCES