Wound Healing After Transoral Angiolytic Laser Surgery for Early Glottic Carcinoma

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Objectives/Hypothesis: Wound healing after transoral angiolytic laser surgery for early glottic carcinoma was analyzed to identify factors influencing healing and clinical significance of persistent granulation tissue.

Study Design: Retrospective review.

Methods: A retrospective review of 100 consecutive patients undergoing endoscopic angiolytic laser surgery for T1 and T2 glottic carcinoma was performed. Patients with prior radiation or incomplete data were excluded. Postoperative endoscopic images were analyzed for time to healing, size and location of wound, and presence of granulation tissue. Three blinded, independent raters graded wound appearance and presence of granulation tissue.

Results: Seventy-nine patients healed without need for intervention at a median of 3.5 months. Two patients had office-based ablation of granulation without biopsy and healed. The remaining 19 patients had biopsy for granulation tissue. Wounds that underwent biopsy at >3 months were more likely to contain carcinoma (5/6 patients, 83%) than wounds that were biopsied <3 months (2/13 patients, 15%) (P < .004). Presence of granulation significantly correlated with resection involving anterior commissure (P = .01), >75% vocal fold length (P = .006), and depth into muscle (P = .001). Delayed healing (>3 months) correlated with T2b tumors (P = .02), depth into ligament (P = .002) and anterior commissure involvement (P = .04). T1a carcinomas more commonly healed in <3 months (P = .005).

Conclusions: Many vocal fold wounds heal completely within 3.5 months after angiolytic laser surgery for early glottic carcinoma. Larger and deeper wounds are more likely to heal with granulation tissue. Granulation can resolve without surgical intervention; however, granulation present >3 months warrants biopsy due to increased risk of malignancy.

Key Words: Potassium-titanyl-phosphate laser, early glottic cancer, wound healing, granulation.

Level of Evidence: 4

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INTRODUCTION

Transoral angiolytic laser surgery for early glottic carcinoma utilizing the 532 nm potassium-titanyl-phosphate (KTP) laser (American Medical Systems, Minnetonka, MN) can yield excellent oncologic and voice outcomes.1–4 Vocal fold wounds created by this surgical strategy heal by secondary intention, and progress through various phases of wound healing. Clinical observation during routine postoperative endoscopy has shown that some patients heal rapidly with minimal inflammation, whereas others develop persistent granulation tissue at the surgical site. When granulation tissue persists during healing, regrowth of malignancy must be considered even though this might simply represent a patient’s unique healing process. Detecting carcinoma recurrence is a crucial reason to carefully examine patients postoperatively. However, repeat operative endoscopy with biopsy may result in unnecessary risks and costs to patients who do not have recurrent carcinoma.

The decision to pursue repeat surgery with biopsy of granulation tissue is guided by endoscopic evaluation of the glottis combined with clinical factors and symptoms. Therefore, knowledge about the healing timeline and wound characteristics, specifically the clinical significance of granulation, after KTP laser–assisted ablation of glottic carcinoma is paramount. There is a paucity of literature regarding wound healing after transoral angiolytic laser surgery for early glottic carcinoma, and no prior study evaluated would healing after KTP laser use. The purpose of this study was to determine the significance of granulation tissue formation, in association with the size and depth of the wound, and tumor stage during healing after transoral angiolytic laser surgery for early glottic carcinoma.

MATERIALS AND METHODS

The institutional review board of Massachusetts General Hospital approved this study. The medical records and endoscopic
exams of 100 consecutive patients (95 male, five female) who underwent KTP laser–assisted ablation of early glottic carcinoma (T1a-62, T1b-23, T2a-6, T2b-9) from 2006 to 2017 and met inclusion criteria were retrospectively reviewed. Patients with carcinoma in situ, previous radiation therapy, or inadequate imaging to evaluate wound healing were excluded. Patients underwent office-based laryngoscopy at 4- to 6-week intervals per American Cancer Society guidelines.5 Endoscopic laryngeal findings in combination with patient factors, such as medical comorbidities and clinical history determined need for biopsy versus continued wound observation. Specific factors leading to biopsy included symptomatic granulation, less reliable patient follow-up, concern for carcinoma, and enlarging granulation tissue.

All postoperative endoscopic exams were subjectively analyzed for time to healing or further surgical intervention, size and location of wound, and presence of granulation tissue. Two fellowship-trained laryngologists and one speech language pathologist (specialized in the treatment of voice disorders) independently rated all exams and were provided with photographic examples of the discrete healing states prior to review. Wounds were rated as 1) having an exudate, 2) being inflamed/edematous, 3) developing granulation tissue, or 4) healed completely (Fig. 1). The presence of granulation tissue was correlated to subsequent carcinoma recurrence and compared to depth and extent of resection of the original wound. All raters were blinded to patient medical history, extent of cancer resection, and time since surgery when making their judgments on the ordinal 1 to 4 scale.

Inter-rater reliability was evaluated between the three raters by using a Fleiss kappa across all four categories (for agreement)6 and a Spearman’s rho correlation (for consistency).7 Kappa statistics were computed between pairs of raters, which produced three reliability coefficients (rater 1 vs. rater 2, rater 1 vs. rater 3, and rater 2 vs. rater 3). Traditionally, the kappa statistic can be interpreted as values <0 indicating no agreement, 0.01 to 0.20 as none to slight agreement, 0.21 to 0.40 as fair agreement, 0.41 to 0.60 as moderate agreement, 0.61 to 0.80 as substantial to excellent agreement, and >0.81 as near perfect agreement.8 Spearman’s ρ was computed as a correlation matrix amongst the three raters, and values between 0.2 and 0.39 are considered weak consistency, 0.4 and 0.59 as moderate consistency, 0.6 and 0.79 as strong consistency, and above 0.8 as very strong consistency.8 To look at the effect of clinical factors and surgical parameters on time to healing and development of granulation tissue, a $\chi^2$ test was used with $P < .05$ as statistically significant.

Fig. 1. Endoscopic images of glottic wounds from different patients showing the four discrete healing states that were rated. (A) Exudate. (B) Inflammation/edema. (C) Granulation tissue. (D) Healed completely. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]
RESULTS

Seventy-nine patients healed without further surgical intervention, including 64 patients who never developed granulation tissue. Of the 36 patients who developed granulation tissue, 15 healed without further surgical intervention, two underwent office-based ablation without biopsy and healed, and the remaining 19 patients had biopsy for granulation tissue during repeat microlaryngoscopy with general anesthesia. Wounds that underwent biopsy for granulation tissue during repeat microlaryngoscopy with general anesthesia. Wounds that underwent biopsy at >3 months were more likely to contain carcinoma (5/6 patients, 83%) than wounds that were biopsied <3 months (2/13 patients, 15%) ($\chi^2[1] = 11.07, P = .009$).

Development of granulation tissue correlated with surgical resection involving >75% cord length ($\chi^2[1] = 7.41, P = .006$), resection at the anterior commissure ($\chi^2[1] = 6.82, P = .009$), and depth into muscle ($\chi^2[1] = 11.07, P = .0009$). Wounds that healed without granulation tissue correlated with T1a staging ($\chi^2[1] = 9.87, P = .002$) and subepithelial resection ($\chi^2[1] = 14.98, P = .0001$). Table I summarizes the factors that correlated with granulation tissue formation.

![Graph depicting wound healing](image_url)

**Fig. 2.** Graphic depiction of wound healing after transoral angiolytic surgery for early glottic carcinoma. The bars show the number of patients healed at a specific time, and the line shows the cumulative percent healed. Note the median time to heal was 3.5 months.

**TABLE I.**

| Tumor Staging and Wound Factors Correlated With Presence or Absence of Granulation Tissue |
|---------------------------------|-----------------|-----------------|
|                                 | Total | Granulation | No Granulation |
| Patients                        | 100   | 36           | 64             |
| T1a*                            | 62    | 15           | 47             |
| T1b                             | 23    | 12           | 11             |
| T2a                             | 6     | 3            | 3              |
| T2b                             | 9     | 6            | 3              |
| Depth: subepithelium$^\dagger$   | 48    | 8            | 40             |
| Depth: ligament                 | 29    | 13           | 16             |
| Depth: muscle$^\ddagger$        | 23    | 15           | 8              |
| Anterior commissure$^\S$        | 32    | 17           | 15             |
| >75% vocal fold length$^\S$     | 60    | 28           | 32             |

$^*_{\text{Significant correlation with no granulation: } P < .01.}$

$^\dagger_{\text{Significant correlation with no granulation: } P < .001.}$

$^\S_{\text{Significant correlation with presence of granulation: } P < .001.}$

$^S_{\text{Significant correlation with presence of granulation: } P < .01.}$

The median time to completely heal was 3.5 months (Fig. 2). Healing in less than 3 months correlated with T1a carcinoma ($\chi^2[1] = 3.86, P = .049$). Delayed healing (>3 months) correlated with T2b tumors ($\chi^2[1] = 4.06, P = .02$), resection involving the anterior commissure ($\chi^2[1] = 4.13, P = .042$), and depth of resection to the vocal ligament ($\chi^2[1] = 9.50, P = .002$). Resection into muscle did not correlate with time to healing. Table II summarizes the factors that correlated with time to complete healing.

From the 100 patients, 340 endoscopic exams were rated by all 3 raters. Inter-rater reliability was moderate to excellent in agreement and strong to very strong in consistency (Fleiss $\kappa = 0.51–0.73$ and Spearman’s $\rho = 0.67–0.81$). Furthermore, all reliability coefficients were statistically significant ($P < .001$).

**TABLE II.**

<table>
<thead>
<tr>
<th>Tumor Staging and Wound Factors Correlated With Time to Healing</th>
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<tbody>
<tr>
<td>Healed &lt; 3 Months</td>
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</tr>
<tr>
<td>Patients</td>
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<tr>
<td>T1a*</td>
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<td>Anterior commissure$^\S$</td>
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<td>&gt;75% vocal fold length$^\S$</td>
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Seventy-nine patients were followed to complete healing, whereas 19 patients had a second surgical intervention (biopsy and removal of granulation tissue).

DISCUSSION

Most wounds healed without granulation tissue within 3-4 months after transoral KTP laser-assisted ablation of early glottic carcinoma. In these patients, no further surgery was needed even if the wound took longer to heal. Factors that correlated with earlier healing (<3 months) were T1a carcinomas, and surgery limited to a depth within the subepithelium, which was not surprising given that smaller and more superficial wounds would be expected to heal readily. Patients who healed after 3 months more commonly had surgical depth into ligament and surgery involving the anterior commissure. Perhaps greater risk of cartilage exposure during treatment of carcinoma at the anterior commissure accounts for delayed healing in this subset, as opposed to deeper wounds in the midfold region that less commonly involve exposed cartilage. Seven patients took >6 months to heal and were clear outliers in this regard. These patients lived far away and followed-up at longer intervals or were examined by a local laryngologist initially.
so the actual time to complete healing was likely shorter than was recorded.

Granulation tissue developed in 36 patients, prompting consideration for further surgery with biopsy. The time course of the appearance of granulation varied substantially between patients. Whereas granulation tissue can be a normal part of wound healing, its persistence creates concern for carcinoma recurrence. Fifteen patients resolved

Fig. 3. Endoscopic images of wound healing progression in a patient following potassium-titanyl-phosphate laser-assisted ablation of a T2 carcinoma. (A) Initial lesion extends the entire length of the right vocal fold. (B) Wound at 3 weeks with exudate. (C) Granulation tissue present at 7 weeks. (D) Granulation tissue at 3 months. (E) Wound completely healed with no granulation tissue at 4.5 months. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]
granulation tissue without further intervention, usually because the granulation tissue was localized, superficial, and was clearly resolving by the next follow-up exam. Figure 3 shows endoscopic images of a typical patient whose granulation tissue was not biopsied. The granulation tissue was not concerning in this patient because it improved at each exam and resolved quickly. Two patients underwent laser ablation of granulation tissue in the office without biopsy (one had medical comorbidities that precluded a return trip to the operating room, and one opted for office treatment as personal preference and travel considerations). Both healed without further granulation tissue formation and did not develop recurrent carcinoma.

In 19 patients, the presence of granulation tissue prompted additional surgery for biopsy. Deciding factors for surgical intervention included clinical concern for persistent malignancy, patient desire for removal, or dysphonia and/or dyspnea related to granulation. Features concerning for recurrent carcinoma are not always apparent based on appearance of granulation tissue alone, as shown in Figure 4. Whereas both patients underwent biopsy with similar-appearing granulation tissue, one result was benign (Fig. 4A,B) and the other was malignant (Fig. 4C,D). When granulation tissue was still present beyond 3 months, biopsy was significantly more likely to contain recurrent carcinoma (5/6 patients had carcinoma that was treated effectively at the second surgery). Based on this finding, the surveillance strategy for early glottic carcinoma patients with granulation tissue involves careful monitoring of the wound up to 3 months, and immediate surgery with biopsy when granulation tissue persists beyond 3 months. Patients are educated about wound healing preoperatively and throughout the follow-up period so they can anticipate and prepare for intervention if needed.

Wound healing in this cohort of patients was certainly influenced by the exclusive use of the 532nm KTP laser. Thermal spread beyond the treatment site can delay healing and thereby facilitate granulation tissue formation regardless of the depth of resection. For example, histopathologic investigations of healing after laser surgery have identified differences between the

Fig. 4. Endoscopic images from two patients who underwent biopsy of granulation tissue. (A, B) Benign granulation at (A) 1 month and (B) 3 months when biopsy was done. (C, D) Carcinoma in a patient with granulation at (C) 3 months and (D) 9 months when biopsy was done. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]
carbon dioxide (CO₂) laser and KTP laser. In a histologic study with rats, Carew et al. demonstrated increased depth of wound healing and decreased wound tensile strength in KTP-created wounds as compared to CO₂ laser and scalpel at 10 days after tongue incision. On a cellular level, Mallur et al. noted that KTP damage of normal vocal cords induced unique matrix metalloproteinases expression, which may help remodel the lamina propria and create less fibrosis during wound healing. The unique thermal effects of the KTP laser compared with other surgical tools can create granulation tissue that must be interpreted and managed appropriately.

Although we believe this to be the first study to analyze the healing timeline and wound characteristics after KTP laser–assisted ablation of glottic carcinoma, other studies have investigated the endoscopic evaluation of healing after early glottic carcinoma surgery. Shen et al. performed a prospective evaluation of healing in 29 patients after CO₂ laser cordectomy for T1 glottic carcinoma. They identified a stabilized vocal cord at an average of 88.1 days and recommend observation for up to 4 months after surgery. Delayed healing correlated with more extensive surgery, as defined by European Laryngological Society cordectomy grade IV or V. Jeong et al. reported an epithelial “stabilization” at a median of 57 days, with 80% of patients healed at 100 days in patients undergoing CO₂ laser cordectomy for T1 glottic cancer. Patients with delayed healing beyond 100 days were found to have a recurrence rate of 33%, so continued observation to 3 months was recommended. This study, which also includes T2 carcinoma, compares favorably with slightly longer time to healing (average of 3.5 months).

The significance of granulation tissue formation after transoral glottic CO₂ laser surgery in patients with Tis-T3 glottic carcinoma was previously reported by Rioja et al., who noted a 53.8% granulation rate at 1 month, as opposed to a 35% granulation rate in this study. The difference may be due to varied tissue effects between the KTP and CO₂ lasers, higher TNM staging within their cohort, or differences in rater evaluation. Interestingly, Rioja’s study excluded anterior commissure involvement, which was relatively common in our study and positively correlated with development of granulation tissue.

Limitations of this study include the retrospective design, lack of control over voice use throughout the entire healing period, and lack of assessment of other factors of wound healing such as the presence of medical comorbidities (diabetes, reflux disease, and peripheral vascular disease). Patients’ return for surveillance exams often varied, although every patient included in this series followed-up beyond final healing or until further surgical intervention. Therefore, it is feasible that our timeline assessment of healing overestimates the duration of healing by up to 6 weeks. Three independent blinded raters assessed endoscopic healing. In general, the agreement between the laryngologists was greater than between either laryngologist and speech language pathologist. This is likely related to greater clinical experience of postsurgical assessment by laryngologists. Overall, inter-rater reliability for the primary healing states of granulation and healed were moderate to excellent in agreement.

CONCLUSION

Many vocal fold wounds heal completely within 3.5 months after 532nm KTP laser–assisted surgery for early glottic cancer. Larger and deeper wounds are more likely to heal with granulation tissue. Granulation can resolve without surgical intervention; however, granulation present >3 months warrants biopsy due to increased risk of malignancy.

BIBLIOGRAPHY