Treatment Results of Carcinoma In Situ of the Glottis

An Analysis of 82 Cases

Quynh-Thu Le, MD; Robert Takamiya, MD; Hui-Kuo Shu, MD; Melanie Smitt, MD; Mark Singer, MD; David J. Terris, MD; Willard E. Fee, MD; Don R. Goffinet, MD; Karen K. Fu, MD

Objectives: To evaluate the results of different treatment modalities for carcinoma in situ of the glottis, and to identify important prognostic factors for outcome.

Design: Review of 82 cases treated definitively for glottic carcinoma in situ between 1958 and 1998. The median follow-up for all patients was 112 months, and 90% had more than 2 years of follow-up.

Setting: Academic tertiary care referral centers.

Intervention: Fifteen patients were treated with vocal cord stripping (group 1), 13 with more extensive surgery (group 2) including endoscopic laser resection (11 patients) and hemilaryngectomy (2 patients), and 54 with radiotherapy (group 3). Thirty patients had anterior commissure involvement and 9 had bilateral vocal cord involvement. Radiotherapy was delivered via opposed lateral fields at 1.5 to 2.4 Gy per fraction per day (median fraction size, 2 Gy), 5 days per week. The median total dose was 64 Gy, and the median overall time was 47 days.

Main Outcome Measures: Initial locoregional control (LRC), ultimate LRC, and larynx preservation.

Results: The 10-year initial LRC rates were 56% for group 1, 71% for group 2, and 79% for group 3. Of those who failed, the median time to relapse was 11 months for group 1, 17 months for group 2, and 41 months for group 3. Univariate analysis showed that the difference in initial LRC rates between groups 1 and 3 was statistically significant ($P = .02$), although it was not statistically significant on multivariate analysis ($P = .07$). Anterior commissure involvement was an important prognostic factor for LRC on both univariate ($P = .03$) and multivariate ($P = .04$; hazard ratio, 1.6) analysis, and its influence appeared to be mainly confined to the surgically treated patients (groups 1 and 2). The 10-year larynx preservation rates were 92% for group 1, 70% for group 2, and 85% for group 3. Anterior commissure involvement was the only important prognostic factor for larynx preservation ($P = .01$) on univariate analysis. All but 2 patients in whom treatment failed underwent successful salvage surgery. Voice quality was deemed good to excellent in 73% of the patients in group 1, 40% in group 2, and 68% in group 3.

Conclusions: Treatment of carcinoma in situ of the glottis with vocal cord stripping or more extensive surgery or radiotherapy provided excellent ultimate LRC and comparable larynx preservation rates. Anterior commissure involvement was associated with poorer initial LRC and larynx preservation, particularly in the surgically treated patients. The choice of initial treatment should be individualized, depending on patient age, reliability, and tumor extent. Pretreatment and posttreatment objective evaluation of voice quality should be helpful in determining the best therapy for these patients.


Carcinoma in situ (CIS) of the glottic larynx is part of the spectrum of premalignant changes primarily associated with cigarette smoking.1 Histologically, it is described as a full-thickness epithelial replacement by cells with malignant cytologic features without evidence of invasion through the basement membrane.2 It is a relatively rare entity, with an annual incidence rate of 0.4 per 100,000 persons.3 Approximately 25% to 30% of laryngeal CIS will progress to invasive tumors, with untreated cases transforming at the highest rates (33.3%-90.0%).4-5

The optimal approach to CIS treatment has been controversial. There has been considerable disagreement as to the initial approaches to these patients, whether it be stripping, laser surgery, cordectomy, radiotherapy (RT), or even watchful waiting. Most series reported on patients treated with either RT alone6-12 or conservative surgery alone.13-15 Those that included both treatment modalities are generally small,16,17 and some included patients with early invasive T1 to T2 carcinomas.18
PATIENTS AND METHODS

Between May 1, 1958, and May 1, 1998, eighty-two patients received definitive treatment for CIS of the glottis at the foregoing 2 institutions. All patients underwent direct laryngoscopy and tumor biopsy or stripping of the vocal cord at diagnosis. All pathology slides were reviewed by either Stanford or University of California, San Francisco, pathologists. Patients who were treated with stripping alone or who had more than 1 stripping procedure performed for CIS before RT were classified as the vocal cord stripping group (group 1; 15 patients). Those who underwent laser excision, cordectomy, hemilaryngectomy, or total laryngectomy immediately after a diagnostic biopsy or stripping were classified as the “more extensive surgery” group (group 2; 13 patients). Those who received RT after biopsy or only 1 stripping procedure were classified as the RT group (group 3; 54 patients).

Table 1 shows the patient and tumor characteristics for the 3 treatment groups. Group 2 had a higher percentage of patients with anterior commissure (AC) involvement and group 3, a higher percentage of patients with bilateral vocal cord involvement. The median follow-up for all patients was 112 months (range, 2.3-358.0 months), and it was similar for all 3 groups. The minimum follow-up was more than 2 years in 74 patients (90%) and more than 5 years in 56 patients (68%). All initial treatments were delivered at either Stanford University or University of California, San Francisco. Within group 1, two patients had 1 stripping procedure, 6 had 2, 5 had 3, and 2 had 4. Within group 2, 11 patients had more than 1 stripping procedure performed before radiotherapy (RT) (vocal cord stripping group); group 2, those who underwent laser excision, cordectomy, hemilaryngectomy, or total laryngectomy immediately after diagnostic biopsy or stripping (more extensive surgery group); and group 3, those who received RT after biopsy or only 1 stripping procedure (RT group).

This retrospective study was conducted at Stanford University, Stanford, Calif, and the University of California, San Francisco, to determine the impact of treatment modality on locoregional control (LRC) and larynx preservation.

Table 1. Patient Characteristics by Treatment Group†

<table>
<thead>
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<th>Characteristics</th>
<th>Treatment Group†</th>
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<tr>
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<td>1</td>
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<tr>
<td>No. of patients</td>
<td>15</td>
</tr>
<tr>
<td>Sex, No. (%) M</td>
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<td>Age, y</td>
<td>48-85</td>
</tr>
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<td>Median</td>
<td>66</td>
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<td>Range</td>
<td>4 (27)</td>
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<tr>
<td>AC involvement, No. (%)</td>
<td>1 (7)</td>
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<td>Bilateral TVC involvement, No. (%)</td>
<td>87</td>
</tr>
<tr>
<td>Follow-up, mo</td>
<td>2-209</td>
</tr>
</tbody>
</table>

†Group 1 included patients treated with vocal cord stripping alone or who had more than 1 stripping procedure performed before radiotherapy (RT) (vocal cord stripping group); group 2, those who underwent laser excision, cordectomy, hemilaryngectomy, or total laryngectomy immediately after diagnostic biopsy or stripping (more extensive surgery group); and group 3, those who received RT after biopsy or only 1 stripping procedure (RT group).

RESULTS

LOCOREGIONAL CONTROL

At last follow-up, treatment had failed in 19 patients: 6 (40%) in group 1, three (23%) in group 2, and 10 (18%) in group 3. Invasive cancer was found in 15 patients: 3 (20%) in group 1, three (23%) in group 2, and 9 (16%) in group 3. The initial site of failure was in the glottis only in 17 patients (invasive cancer in 13 and CIS in 4) and in the glottis and cervical lymph nodes in 2 patients. There was no isolated nodal failure without local recurrence, and there was no distant metastasis. Of those in whom treatment failed, the median time to relapse was 11 months for group 1 (range, 6-25 months), 17 months for group 2 (range, 3-48 months), and 41 months for group 3 (range, 6-134 months). Six patients were placed in the failure category more than 5 years after RT, and many continued to smoke after the completion of treatment. It is unclear whether these new lesions represented second primary tumors or late relapses. However, for the purpose of this analysis, they were scored as late failures. The 5- and 10-year Kaplan-Meier estimates of LRC rates were both 56% for the stripping group, 71% for the more extensive surgery group, and 90% and 79%, respectively, for the RT group (Figure 1). Within group 2, the 5- and 10-year LRC rates for the 11 patients treated with endoscopic laser resection were both 80%.

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Table 2 shows the LRC rates in relation to a number of potential prognostic factors for all patients. These include age, sex, AC involvement, unilateral vs bilateral true vocal cord involvement, and type of treatment. Involvement of the AC was a significant factor on univariate analysis (P=.03). Subset analysis disclosed that the impact of AC involvement was more significant for groups 1 and 2 than for group 3. Within the first 2 groups, the 10-year LRC rates were 37% and 80% for patients with and without AC involvement, respectively (P=.05). Within the RT group, the rates were 73% and 82% for patients with and without AC involvement, respectively (P=.28). In addition, there was a trend toward poorer initial LRC with vocal cord stripping alone (P=.07). Pairwise comparison showed a significant difference in initial LRC between groups 1 and 3 (P=.02) but not between groups 2 and 3 or between groups 1 and 2.

A multivariate analysis in which the patients in groups 1 and 2 were combined was carried out by means of the Cox regression hazard model. Involvement of the AC was found to be an independent factor for LRC, with a P value of .04 and a hazard ratio of 1.6 (95% confidence interval, 1.02-2.5). Although treatment modality was not a significant factor, it favored RT, with a P value of .07 and a hazard ratio of 0.4 (95% confidence interval, 0.2-1.03).

We evaluated a number of potentially important prognostic factors for LRC in patients treated with RT as the initial management. These included age, AC involvement, unilateral vs bilateral true vocal cord involvement, fraction size, total dose, radiation overall time, treatment field size, beam energy, and hemoglobin level. Table 3 shows the LRC in relation to these variables. None of the tested variables was significant on univariate analysis. On multivariate analysis, none of the variables reached statistical significance, except for a trend toward inferior LRC with increasing overall time (P=.10; hazard ratio, 1.18 per day). Since there was an interaction between total dose, overall time, and fraction size, we generated scatterplots (Figure 2) to evaluate the impact of total dose, fraction size, and overall time on initial LRC. As shown in Figure 2A, there was no relationship between total dose or fraction size and initial tumor.
control. In patients treated with an overall time of 50 days or less, the total dose, within the range evaluated, had no significant impact on LRC. Both of the 2 patients treated with an overall time of more than 50 days and a total dose of 60 Gy or less had treatment failure.

**SALVAGE THERAPY**

Salvage therapy for each treatment group and the number of cases salvaged are shown in Table 4. All but 2 patients in whom treatment failed underwent successful salvage with either RT or more extensive surgery. Of these 2 patients, one was initially treated with RT in 1958. He continued to smoke and drink after therapy and developed an invasive cancer involving the same true vocal cord in 1967, treated with hemilaryngectomy. He then developed nodal relapse and eventually died of locoregional progression more than 10 years after the initial diagnosis, despite additional salvage surgery and RT. In the second patient 3 stripping procedures had failed, and the patient received salvage RT for a bulky CIS relapse, although microinvasion could not be ruled out. He had treatment failure 2 years later with invasive cancer and was treated with total laryngectomy, neck dissection, and additional RT. He eventually died of tumor progression in the base of the tongue despite the use of salvage chemotherapy. After salvage, the 10-year estimate of ultimate LRC rates were 90% for the stripping group, 100% for the more extensive surgery group, and 96% for the RT group.

**LARYNX PRESERVATION AND VOICE QUALITY**

The larynx was preserved in 14 of 15 patients in the stripping group, 10 of 13 patients in the more extensive surgery group, and 47 of 54 patients in the RT group. The 10-year larynx preservation rates were 92%, 70%, and 85% for groups 1, 2, and 3, respectively (Figure 3). Univariate analysis disclosed that AC involvement was a potential prognostic factor for larynx preservation, favoring patients with no AC extension. The 10-year larynx preservation rates were 71% and 93% for those with and without AC involvement, respectively (P = .01; Figure 4A). Subset analysis showed that the difference was highly significant for the surgically treated patients (groups 1 and 2); the 10-year estimates of larynx preservation were 57% and 100% for those with and without AC involvement, respectively (P = .007; Figure 4B). Within the RT group, AC involvement was not a significant factor for larynx preservation; the 10-year larynx preservation rates were 89% and 93% for those with and without AC involvement, respectively (P = .30; Figure 4C). No other variables evaluated, including age, sex, bilateral vo-

![Figure 2](http://archotol.jamanetwork.com/data/journals/otol/9773/) Initial locoregional control in relation to total dose and fraction size (A) and total dose and irradiation overall time (B). LRC indicates locoregional control.

![Figure 3](http://archotol.jamanetwork.com/data/journals/otol/9773/) Kaplan-Meier estimates of larynx preservation for all patients. Groups are defined in the second footnote to Table 1.
cal cord involvement, and treatment type, was significant on univariate analysis. Multivariate analysis was not carried out because of the small number of events.

Voice quality was scored as determined by the treating physicians and the patients. The results are shown in Table 5. It was deemed good to excellent in 11 (73%) of 15 patients in group 1, six (46%) of 13 patients in group 2, and 37 (69%) of 54 patients in group 3.

**LATE COMPLICATIONS**

Late treatment-related complications occurred in 7 patients, 6 of whom were in the RT group. One patient had marked arytenoid scarring after multiple stripings and laser resections. One patient had marked chronic laryngeal edema for 1 year after completion of RT, requiring corticosteroid therapy. This patient received a total dose of 60 Gy in 30 fractions to a field size of 10 × 13 cm and continued to smoke throughout and after treatment. Two patients developed AC webbing at 2 and 3 years after RT, 1 patient had laryngeal fibrosis documented on biopsy associated with poor voice, 1 patient had chronic edema and a fixed true vocal cord 3 years after treatment, and 1 patient had laryngeal fibrosis after reirradiation for a second primary tumor on the epiglottis.

**SURVIVAL**

At last follow-up, 33 patients had died: 2 of recurrences and 31 of intercurrent illnesses. The 10-year disease-specific survival for the entire group was 98%, and the 10-year overall survival was 78%. Figure 5 shows the survival curves for the surgery (groups 1 and 2) and RT groups. There was no difference in survival between the 2 groups of patients.

Secondary malignant neoplasms were documented in 23 patients, some with more than 1 site. There were 2 skin cancers (both outside of the treatment fields), 2 melanomas, 5 head and neck cancers (1 oral tongue cancer, 1 posterior pharyngeal wall cancer at 3 years after RT, 2 epiglottis cancers at 1 and 28 years after RT, and 1 nasopharyngeal cancer), 1 thyroid cancer, 6 lung cancers, 8 prostate cancers, 1 bladder cancer, 1 colon cancer, and 1 meningioma.

**COMMENT**

Management of CIS of the glottis remains controversial. Treatment options include vocal cord stripping, endoscopic laser surgery, cordectomy, hemilaryngectomy, and RT. Small, previously untreated CIS lesions may be con-
trolled by vocal cord stripping alone. Advantages of stripping procedures include a 1-session therapy (rather than a 6- to 7-week course with RT), the ability to remove all abnormal-appearing tissue to exclude invasive cancer, minimal treatment-related morbidity, and ability to preserve vocal cord function. When stripping fails, the salvage rate with RT is excellent. However, local recurrence is frequent with stripping alone (ie, RT, laser resection, or cordectomy) for salvage. Similarly decreased voice quality and the inability to treat large tumors with AC extension by a single procedure. The initial control rates with endoscopic laser excision ranged from 50% to 100%, although most authors report rates higher than 80% (Table 6). In the present series, there were only 2 local failures in the 11 patients treated with endoscopic laser surgery. Thus, the crude LRC rate was 82% and the 10-year Kaplan-Meier estimate of LRC was 80%. The majority of cases in which treatment fails can be salvaged with RT, and the ultimate LRC rates should be greater than 90%. Drawbacks of laser surgery include potentially decreased voice quality and the inability to treat large tumors with AC extension by a single procedure.

In general, institutions using RT as primary therapy in these patients have reported excellent LRC rates, similar to those for T1 tumors (Table 6). However, recurrence rates after RT are variable, and some authors have suggested that CIS may be “intrinsically more radioresistant” than invasive true vocal cord tumors. The poorest RT results came from 2 small series (by Smith and Lockey37 and Miller and Fisher24) that reported only 45% to 50% LRC rates. In Smith and Lockey’s series, only 56% of the patients achieved LRC by vocal cord stripping alone. Advantages of stripping alone (resection, or cordectomy) for salvage. Similar to other reports in the literature, most patients in this series required an average of 2 stripping procedures to maintain LRC, and the vocal cords have the potential of becoming thickened and the voice hoarse with repeated stripping.

Conservative endoscopic laser excision of vocal cord tumors was popularized in 1975, when Strong introduced the carbon dioxide laser for this purpose. Laser excision is convenient and exact. The lack of superficial bleeding makes it easy for the endoscopist to control surgical margins and the depth of excision. The initial control rates with endoscopic laser excision ranged from 50% to 100%, although most authors report rates higher than 80% (Table 6). In the present series, there were only 2 local failures in the 11 patients treated with endoscopic laser surgery. Thus, the crude LRC rate was 82% and the 10-year Kaplan-Meier estimate of LRC was 80%. The majority of cases in which treatment fails can be salvaged with RT, and the ultimate LRC rates should be greater than 90%. Drawbacks of laser surgery include potentially decreased voice quality and the inability to treat large tumors with AC extension by a single procedure.

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### Table 6. Locoregional Control of Glottic CIS by Treatment Types: Survey of the Literature*

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<th>Source, y</th>
<th>Stripping</th>
<th>Laser Surgery</th>
<th>RT</th>
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<td></td>
<td>No. of Patients</td>
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<td>% ULRC</td>
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<td>Elman et al,24 1979</td>
<td>8</td>
<td>50 (4/8)</td>
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<td>Harwood et al,14 1980</td>
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<td>Hintz et al,5 1981</td>
<td>27</td>
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<td>93</td>
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<td>Gillis et al,24 1983</td>
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<td>Maran and</td>
<td>23</td>
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<td>Crissman et al,20 1988</td>
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* ILRC indicates locoregional control; ULRC, ultimate locoregional control; RT, radiotherapy; NR, not reported; and NA, not applicable.
† Some patients underwent biopsy only.
‡ Twelve patients underwent laser excision in addition to stripping. Seven patients had microinvasive carcinoma.
§ Some patients underwent vocal cord stripping only.
|| Ten-year actuarial rates.
ure with an invasive carcinoma. In Miller and Fisher’s study, RT was used for large, extensive lesions that, in many cases, involved both true vocal cords. In addition, in a number of patients, RT was used for salvage after multiple endoscopic procedures for recurrences. In our experience, excellent LRC was achieved with definitive RT. Unlike endoscopic surgical failures, which generally occur within 1 to 2 years after therapy,24,25 many patients in our series had late relapses. It is unclear whether these lesions represented second primary tumors or late recurrences. In either case, long-term follow-up is important for these patients, and chemoprevention, once better defined, may have a role in their treatment.

Data from our series showed that RT resulted in the highest initial LRC rate, followed by more extensive surgery and vocal cord stripping. The difference in LRC rates between RT and vocal cord stripping was statistically significant on univariate analysis but not on multivariate analysis. Most patients who had relapses underwent successful salvage with either additional surgery or RT, resulting in similar rates of larynx preservation and ultimate LRC. Voice quality, as shown in Table 5, was similar for the RT and the stripping groups. Therefore, the choice of initial treatment of a patient with CIS of the vocal cords should be individualized on the basis of patient age, reliability, and the extent of the lesion. Our recommendation for treatment of any hyperkeratotic or dysplastic lesion is complete removal via microlaryngoscopy with or without the laser, so that all abnormal tissues can be appropriately oriented and examined for proper pathological diagnosis. Assuming only CIS is found, the patient is either followed up or treated with RT, according to patient and/or physician preference. Within our group, there are differences of opinion. Some prefer to treat with repeated microlaryngoscopy and excision until or if invasive cancer is found. The patient can then be treated with either more extensive laser excision or RT, depending on tumor extent and voice quality. Others prefer RT at the onset of treatment for CIS.

Involvement of the AC has been associated with a high risk of an invasive recurrence in patients treated with endoscopic surgery for CIS. Myssiorek et al31 observed a 92% conversion rate to invasive cancer in lesions involving the AC, compared with 17% for tumors limited to the mobile portion of the vocal fold. A similar high local failure rate was observed in the present series. Only 37% and 57% of the patients with AC involvement treated surgically (groups 1 and 2) had LRC and larynx preservation, respectively, at 10 years. Many patients with AC involvement may have had a larger tumor burden anteriorly and, in some cases, unrecognized subglottic extension. These patients appeared to have a higher risk of treatment failure, and their initial treatment should include RT delivered in a way that ensures adequate tumor coverage anteriorly. Our current policy is to omit the use of wedges in patients with AC involvement and to use 4 MV of x-rays whenever possible. If 6 MV of x-rays is used, bolus material is added to the skin overlying the anterior commissure to ensure adequate dosage delivery to this area.

We did not observe any obvious relationship between initial LRC rates and treatment variables such as age, sex, hemoglobin level, tumor dose, fraction size, treatment field size, or beam energy in patients treated with definitive RT. However, the number of patients might be too small to allow for meaningful analysis. There was a trend toward inferior LRC with prolonged overall RT time on multivariate analysis. The dose-time scatterplot showed that neither of the 2 patients treated with overall time of more than 50 days and total dose of 60 Gy or less achieved LRC. This suggests that higher total doses are necessary when the overall time is prolonged. For patients treated with a short overall time, a total dose of 50 Gy or more, given in fractions of greater than 2 Gy, may be adequate for tumor control. The University of Florida at Gainesville46 reported a 5-year LRC rate of 93% for patients treated with 56.2 Gy at 2.25 Gy per fraction per day. Recently, Spayne et al38 reported a 98% 5-year actuarial LRC rate in 67 patients treated with 51 Gy in 20 fractions over 4 weeks.

Voice quality was deemed good to excellent in more than two thirds of the patients in both the stripping and RT groups. It was worse, however, in patients treated by more extensive resections. Since this is a retrospective study in which data on voice quality were obtained from the treatment records, the results are subject to possible bias and should be viewed with caution. Hirano et al39 objectively evaluated vocal function in a small group of patients treated with either RT or laser resection for invasive T1a carcinoma of the glottis. They found that laser resection, when compared with RT, was associated with a slightly higher degree of hoarseness, more incomplete vocal closure, and more diminution of vocal fold vibration, especially when the vocalis muscle was removed. However, as far as conversational voice is concerned, there was little difference in vocal function. No such study has been performed for CIS of the glottis. Prospective objective evaluation of voice quality is needed to determine voice quality before and after either RT or repeated endoscopic surgeries for these tumors.

CONCLUSIONS

Our data showed that either vocal stripping, or more extensive surgery or RT provided excellent LRC and larynx preservation rates for CIS of the glottis. There was a trend toward fewer local relapses in patients treated by RT in comparison with those treated by vocal cord stripping. Almost all patients in whom treatment failed underwent successful salvage. Anterior commissure involvement was associated with poorer initial LRC and larynx preservation, particularly in the surgically treated patients. The choice of initial treatment should be individualized depending on patient age, reliability, tumor extent, and physician expertise. Pretreatment and posttreatment objective evaluation of voice quality should be helpful in determining the best therapy for patients with glottic CIS.

Accepted for publication March 11, 2000.
Presented at the 41st annual meeting of the American Society for Therapeutic Radiology and Oncology, San Antonio, Tex, November 3, 1999.
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