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AJNR Am J Neuroradiol 1995, 16 (4) 655-662
http://www.ajnr.org/content/16/4/655

Can Pretreatment CT Predict Local Control of T2 Glottic Carcinomas Treated with Radiation Therapy Alone?

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PURPOSE: To determine whether pretreatment CT can predict local control of T2 squamous cell carcinoma of the glottic larynx treated with radiation therapy alone. **METHODS:** Pretreatment CT studies were retrospectively evaluated by two head and neck radiologists in 28 patients with T2 squamous cell carcinoma of the glottic larynx treated with definitive radiation therapy. All patients were followed for a minimum of 2 years. A tumor score was calculated based on the CT findings of tumor involvement of the following areas: the anterior commissure, the contralateral true vocal cord, the arytenoid face, the interarytenoid region, the laryngeal ventricle, the paraglottic space at the true and false vocal cord levels, and the subglottic region. Tumor volumes based on pretreatment CT were measured in each patient using a computer digitizer. Statistical analysis was performed using the independent sample *t* test, Wilcoxon's rank sum test, and Fisher's Exact Test. **RESULTS:** There was no statistically significant relationship between tumor volume or tumor score and outcome of the T2 glottic tumors treated with definitive radiation therapy in this series. The overall local control rate was 82%. There were no treatment complications that resulted in loss of laryngeal function. **CONCLUSIONS:** Like low-volume supraglottic and T3 glottic carcinomas, T2 glottic squamous cell carcinoma is likely (82%) to be controlled with definitive radiation therapy. Failure to control the primary tumor is attributable to factors other than volume, which may not be detectable on CT, such as tumor-host biological factors. Pretreatment CT, however, is beneficial for detecting submucosal spread across the ventricle and subglottic extension, which might contraindicate vertical hemilaryngectomy and might not be apparent on endoscopic examination.

Index terms: Carcinoma; Larynx, neoplasms; Computed tomography, in treatment planning; Therapeutic radiology, treatment planning

AJNR Am J Neuroradiol 16:655–662, April 1995

The optimal treatment for T2 glottic carcinomas is controversial, because these lesions often are suitable for treatment with either conservation surgery or radiation therapy (1). Radiation therapy has proved to be an effective treatment, with local control rates similar to that achieved with partial laryngectomy. Radiation therapy provides a noninvasive treatment alternative, which allows preservation of laryngeal function. Additionally, patients not suitable for hemilaryngectomy may be effectively treated with radiation therapy. Because of these advantages and dispersion of centers capable of modern treatment planning and delivery, a growing number of patients are being treated with radiation therapy alone.

The selection criteria for treatment with definitive radiation therapy have historically been based primarily on clinical examination and the patient's willingness to return for frequent follow-up visits (2). However, surgical salvage performed as a result of local failure after radiation therapy has a greater complication rate when compared with a similar procedure per-

Received June 29, 1994; accepted after revision November 2.

Dr Mukherji received the Head and Neck Radiologist in Training Award at the 1994 meeting of the American Society of Head and Neck Radiology in Washington, DC, where this paper was presented as a poster.

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AJNR 16:655–662, Apr 1995 0195-6108/95/1604–0655

formed on the unirradiated neck (2). Some groups suggest that up to one third of patients undergoing salvage laryngectomy for radiation therapy failures experience a significant complication (2). Therefore, it would be helpful to be able to select those patients with favorable lesions amenable to radiation therapy, thus reducing the number of patients undergoing salvage laryngectomy with its inherent potential risks. Additionally, it would be beneficial to identify those patients with a higher likelihood of failure to provide more careful clinical monitoring of the primary site, perhaps assisted by periodic computed tomographic (CT) examinations.

Pretreatment CT volumetric analysis of the primary tumor has been shown to be an effective predictor of local control in a variety of laryngeal tumors treated with radiation therapy alone. Lee et al demonstrated significant differences in local control rates for T3 glottic tumors based on pretreatment CT tumor volume and analysis of the lesion spread pattern (2). Tumors with volumes less than or equal to 3.5 cm^3 had a higher likelihood of control than tumors with volumes greater than 3.5 cm^3 (92% versus 33%, respectively). Tumors with involvement of more anatomic subsites had significantly reduced likelihood of control (2).

In a similar study, Freeman et al were able to identify those patients with supraglottic carcinomas who had a higher likelihood of local control based on pretreatment tumor volume (3). Tumors with volumes of 6 cm^3 or less had an 83% probability of local control; those lesions with volumes greater than 6 cm^3 had only a 46% control rate (3).

The purpose of this study was to evaluate the usefulness of pretreatment CT in stratifying patients with T2 glottic carcinoma into groups with a high versus low likelihood of cure when treated with radiation therapy alone. Specifically, the study attempts to determine whether CT volumetric analysis and/or a tumor score based on the involvement of specific anatomic sites can be used to help predict local control in patients treated with definitive radiation therapy.

Materials and Methods

Twenty-eight patients with T2 squamous cell carcinoma of the glottic larynx were treated with definitive radiation therapy. Patients presenting with clinical T2 lesions based on supraglottic or subglottic extension with normal or partially reduced cord motion were evaluated in the current study. Patients with clinical T1 (tumors confined to the true vocal cord with normal mobility) or T3 (ipsilateral fixed vocal cord) lesions were not included in this study. Malignancies showing evidence of gross thyroid cartilage invasion on initial CT were also excluded. Tumor staging was based on guidelines of the American Joint Committee on Cancer. All patients had clinical and/or radiographic follow-up for a minimum of 2 years after the completion of therapy.

All patients underwent pretreatment contrast-enhanced CT of the larynx (3- to 5-mm-thick contiguous sections; field of view, 16 cm; matrix size, 512 × 512 mm). Studies were performed with the gantry angled parallel to the plane of the true vocal cords. Scans were initially obtained using a breath-hold technique. If the true vocal cords were closed, the studies were repeated in quiet respiration to obtain images of the cords in adduction. All pretreatment studies were retrospectively reviewed by two head and neck radiologists who were blinded to patient outcome. All determinations were based on a consensus. The tumor volumes and the anatomic spread pattern of the tumor as defined by involvement at specific sites were recorded for each patient based on CT findings.

The anatomic sites evaluated included: (*a*) the anterior commissure, (*b*) the contralateral true vocal cord, (*c*) the face of the ipsilateral arytenoid, (*d*) the interarytenoid region (posterior commissure), (*e*) the ipsilateral ventricle, (*f*) the paraglottic space at the true cord level, (*g*) the paralaryngeal space at the false vocal cord level, and (*h*) subglottic spread. A total score was assigned to each tumor based on the number of anatomic sites involved (maximum score, 8). For example, a tumor involving the anterior commissure and adjacent paraglottic space received a tumor score of 2. The amount of subglottic spread was calculated for each tumor by measuring its distance (in millimeters) from a section through the undersurface of the true vocal cord (ie, 5 mm inferior to the free margin of the true cord).

Volumetric analysis was performed on all tumors in the following manner. The primary lesion was outlined on each image in which a mass was present. The tumor outlines were then transferred into a treatment-planning digitizer. The final tumor volumes were generated after correcting for magnification factor and the section thickness. Three tumors were small, superficial lesions, which were not seen on CT. The tumor volume in each of these three lesions was assumed to be 0.5 cm^3 for the purpose of statistical analysis.

All patients were treated with radiation therapy alone. Treatment consisted of continuous course of radiation therapy of once- or twice-a-day fractionation over a 5-week treatment period (total dose, 68 to 74.4 Gy).

Patients were followed for a minimum of 2 years for recurrent disease or treatment complications. Major treatment complications resulting in the loss of a functional larynx were noted. Mild laryngeal pain or hoarseness in a patient with an otherwise normally functioning larynx was thought to represent minor complications.

The statistical comparison of mean tumor volumes in patients for whom treatment locally failed versus those whose tumors were controlled was performed using the independent sample *t* test. The statistical power of the *t* test used to compare mean tumor volumes was assessed retrospectively via the unified power analysis methods of O'Brien and Muller (4). Tumor scores in these two patient groups were compared using Wilcoxon's rank sum test. Fisher's Exact Test was used to compare the incidence of local control versus the presence or absence of involvement of a specific anatomic subsite.

Results

Twenty-three of 28 cases were successfully controlled with radiation therapy alone, resulting in an overall local control rate of 82%. There was no significant difference in mean tumor volume (P = .886) between patients whose tumors were locally controlled (mean volume, 1.59 ± 0.76 cm^3) and patients in whom treatment failed (mean, 1.54 ± 1.06 cm^3) (Fig 1). Volumes of successfully treated tumors ranged from 0.5 to 3.63 cm^3 (Fig 2). The volumes of the tumors that were not controlled were 0.5 cm^3 (n = 2), 1.46 cm^3 (Fig 3), 2.47 cm^3, and 2.75 cm^3.

The association of neoplastic involvement of specific anatomic subsites with local control is summarized in Table 1. There was no specific anatomic site that, when involved by tumor on the pretreatment study, was shown to be a poor prognostic indicator of local control.

The distribution of tumor scores by local control is shown in Figure 4. The tumor scores ranged from 0 to 6. No tumors had scores greater than 6. The scores of tumor for which radiation therapy failed were 4 (n = 2), 1 (n = 1), and 0 (n = 2). Radiation therapy successfully controlled tumors with scores of 6 (n = 2), 5 (n = 1), and 4 (n = 5). There was no significant difference in score between the tumors that were locally controlled and those in which radiation therapy failed (P = .377).

The relationship between local control and the amount of subglottic spread is depicted in Table 2. An increasing amount of subglottic extension was not significantly associated with a decreasing probability of local control. Tumors for which treatment failed had the following amount of subglottic extension: 9 mm (n = 1) and 3 mm (n = 2). Two patients for whom treatment failed had no radiographic evidence of subglottic extension. Tumors with subglottic spread of up to 10 mm (n = 1) and 9 mm (n = 1) were successfully controlled with radiation therapy alone.

Seven of 28 patients had reduced vocal cord mobility on pretreatment physical examination. Six of these 7 patients' tumors were locally controlled at the primary site. In five of 28 patients treatment with definitive radiation therapy failed. Of these 5 patients for whom treatment failed, only 1 patient had impaired mobility of the true vocal cord before the initiation of radiation therapy.

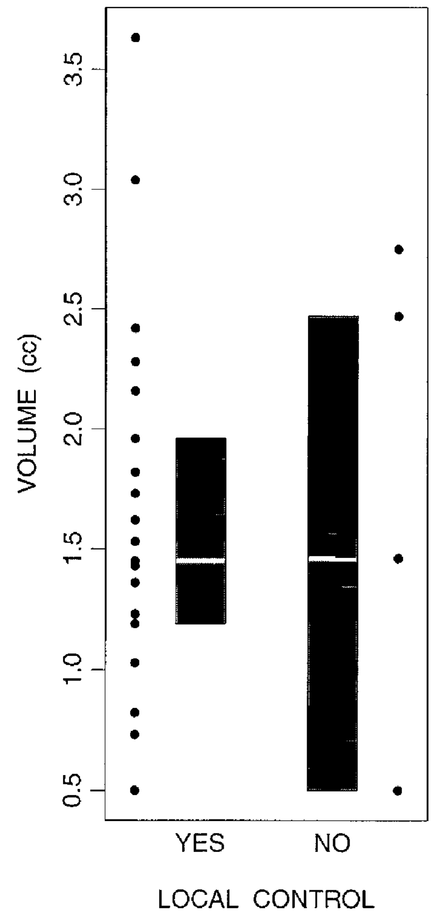
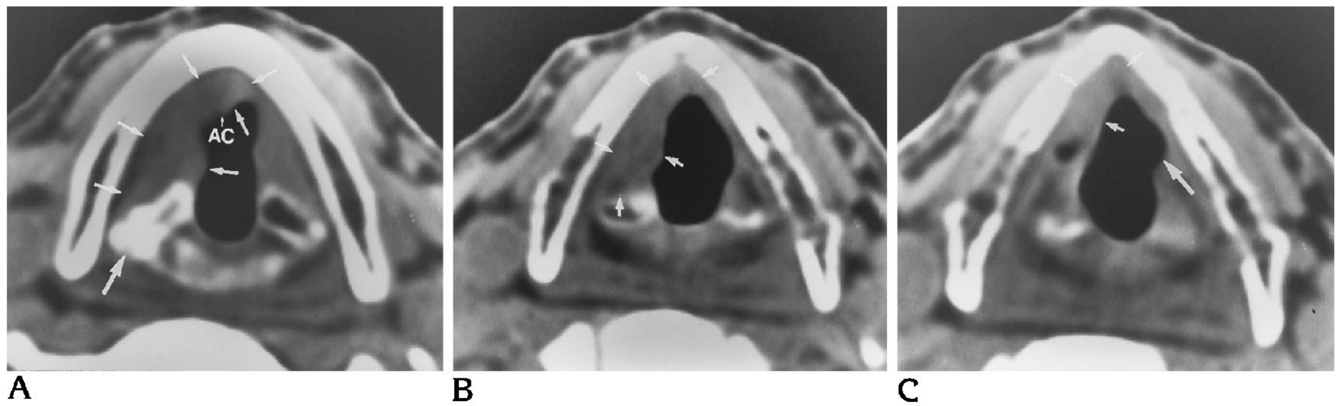


Fig 1. Distribution of tumor volumes by local control is depicted with a combination of scatter points and a modified box plot. The *box* spans the range of tumor volumes from the 25th to 75th percentiles. The *bar* within the box indicates the median tumor volume. There was no significant difference in tumor volumes between patients whose tumors were locally controlled with radiation therapy and those patients for whom treatment failed (P = .886).



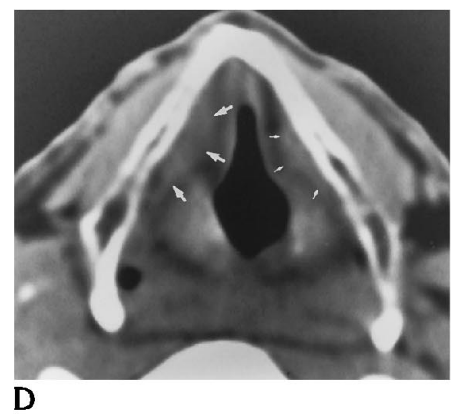


Fig 2. Sequential CT images of a 1.74-cm^3 T2 glottic tumor that was successfully controlled with radiation therapy alone.

A, Axial image at the level of the cricoarytenoid joint shows an infiltrating lesion involving the right true cord, which spreads across the anterior commissure (*AC*) to involve the contralateral true cord (*small arrows*). There is associated sclerosis of the right arytenoid cartilage (*large arrow*).

B, At the superior surface of the true cord, there is continued involvement of the anterior two thirds of the cord (*arrows*) above the anterior commissure.

C, The tumor (*small arrows*) extends superiorly to involve the laryngeal ventricle. Note the normal appearance of the distended laryngeal ventricle on the uninvolved side (*large arrow*).

D, Superiorly, there is enlargement of the lateral thyroarytenoid muscle (*large arrows*) compared with the normal appearance on the uninvolved side (*small arrows*) caused by continued submucosal spread of tumor along the muscle to the paraglottic space at the false cord level. This spread would be a contraindication for treatment with a standard vertical hemilaryngectomy.

Two patients experienced persistent hoarseness after radiation therapy; however, no patient had a major treatment complication (eg, laryngeal necrosis or severe laryngeal edema) resulting in the loss of a tumor-free larynx.

Discussion

The role of CT for imaging laryngeal carcinomas has evolved over the last 10 years as a result of technological advancements, which have decreased scan acquisition time and have improved the ability to obtain high-quality thin-section (1- to 3-mm) images, thus permitting detailed evaluation of the laryngeal anatomy. Several studies have been performed correlating CT findings of laryngeal carcinoma with whole-organ sections. These studies have shown that CT can allow accurate prediction of the site, size, and spread patterns (except for mucosal disease) of laryngeal tumors, thus validating CT as a reliable modality for evaluating the deep extent of laryngeal carcinoma (5–8). Pretreatment imaging has been shown to improve the accuracy of staging and has become complementary to the physical examination for evaluation of laryngeal tumors at many institutions (9–12).

In the current study we evaluated 28 patients treated with definitive radiation therapy with curative intent. The overall cure rate was 82%. This local control rate is similar to that observed by Fein et al in his series of 115 patients irradiated for T2 glottic carcinoma, suggesting that our cohort is representative of the overall patient population (1). None of the patients in this series experienced a major treatment-related complication resulting in the loss of a tumor-free functional larynx. Thus, in our series, the overall local control rate is equal to the likelihood of retaining a functioning larynx for patients treated with radiation therapy. Fein et al observed late complications in only 2 of 115 patients (1.7%) treated with radiation therapy, thereby lending additional support to the supposition that our patient population is a repre-

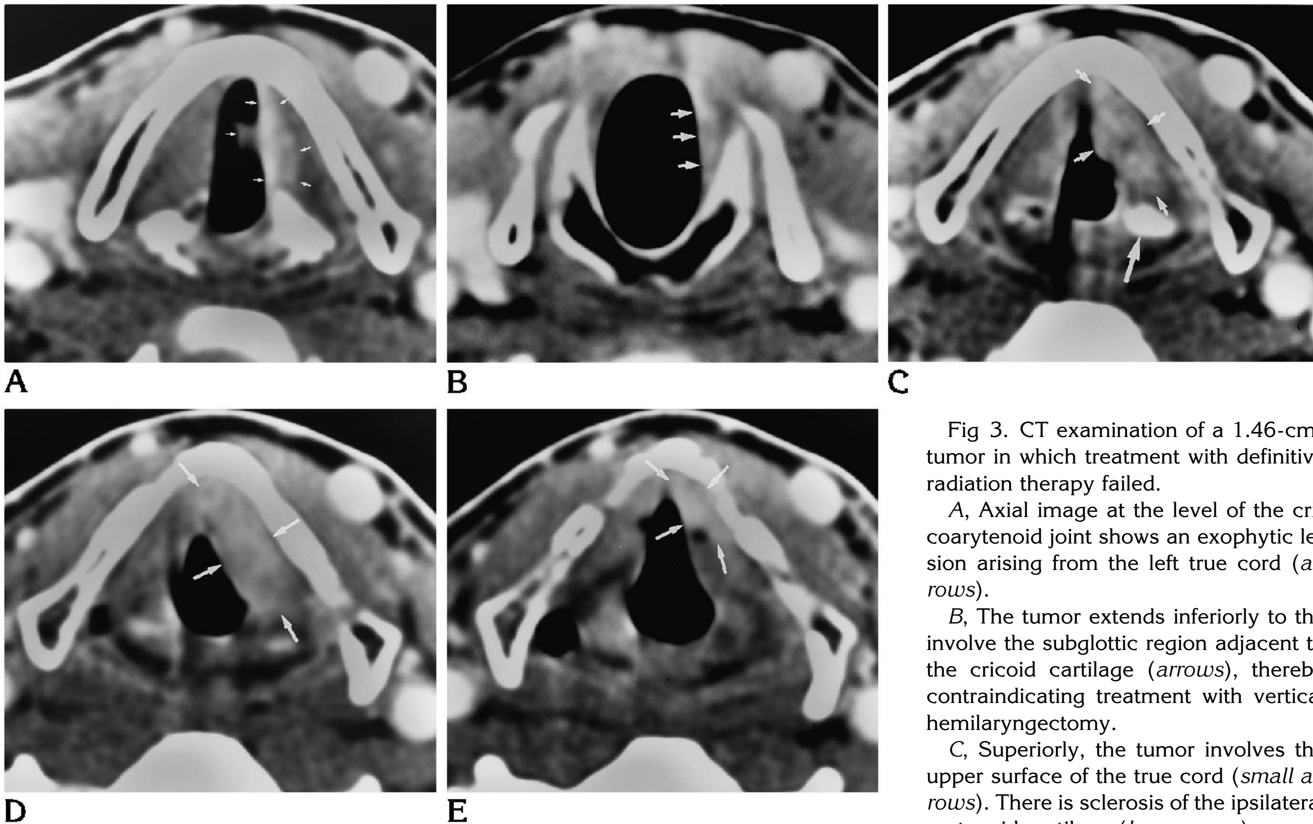


Fig 3. CT examination of a 1.46-cm^3 tumor in which treatment with definitive radiation therapy failed.

A, Axial image at the level of the cricoarytenoid joint shows an exophytic lesion arising from the left true cord (*arrows*).

B, The tumor extends inferiorly to the involve the subglottic region adjacent to the cricoid cartilage (*arrows*), thereby contraindicating treatment with vertical hemilaryngectomy.

C, Superiorly, the tumor involves the upper surface of the true cord (*small arrows*). There is sclerosis of the ipsilateral arytenoid cartilage (*large arrow*).

D, The tumor (*arrows*) continues superiorly to involve the laryngeal ventricle.

E, There is probable extension of the tumor to involve the inferior surface of the false cord (*arrows*).

sentative sample of patients with T2 glottic cancer as a whole (1).

The current results regarding the likelihood of local control as a function of tumor volume or tumor score are similar to those obtained for favorable T3 glottic lesions as previously reported by Lee et al (2). These findings suggest that glottic tumors, T2 or T3, with volumes less than 3.5 cm^3 and tumor scores less than 6 have an 82% to 85% probability of local control with radiation therapy alone. Only one tumor in the current series had a volume greater than 3.5 cm^3 (3.63 cm^3), and two patients had tumor scores greater than 5 (score of 6, n = 2). All three patients were successfully controlled at the primary sites.

Volumetric analysis performed in the current study was obtained directly from images and not from the original raw data. Because of these limitations, there is a certain error rate intrinsic to our volume measurements. We feel our calculated volumes are within 10% to 20% of the actual tumor volume. In reality, however, the exact size of the tumor often cannot be measured at surgery, because tumors often decrease in size immediately after resection. This relatively small degree of error does not adversely affect the statistical results determined by our study. Accurate and reproducible measurements are achievable in experienced hands, and measurements should be made using high-quality studies, which are not degraded by motion or respiratory misregistration artifacts.

Concerns that the number of patients in the present study may have been too small to show a clinically meaningful difference between the mean tumor volumes in patients for whom treatment locally failed and those who were cured are minimal. Based on the sample size and observed standard deviations, the probability of detecting a 1-cm^3 difference in mean tumor volumes at an α-level of .05 was 78%, with 95% confidence limits of 55% to 92%. However, evaluation of a larger patient population would be helpful for further confirmation of our results.

The causes of local failure in the current series are likely attributable to underlying factors

TABLE 1: Local control according to involvement of anatomic subsite on pretreatment CT (28 patients)

Site	Involved?	Local Control (%)	*P* Value
Anterior commissure	Yes	9/9 (100.0)	.14
	No	14/19 (73.7)	
Contralateral true vocal cord	Yes	4/4 (100.0)	1.00
	No	19/24 (79.2)	
Face of arytenoid	Yes	4/4 (100.0)	1.00
	No	19/24 (79.2)	
Interarytenoid space	Yes	1/1 (100.0)	1.00
	No	22/27 (81.5)	
Ventricle	Yes	14/16 (87.5)	.62
	No	9/12 (75.0)	
Paraglottic space, true vocal cord level	Yes	6/8 (75.0)	.61
	No	17/20 (85.0)	
Paraglottic space, false vocal cord level	Yes	6/8 (75.0)	.61
	No	17/20 (85.0)	
Subglottic region	Yes	17/20 (85.0)	.61
	No	6/8 (75.0)	

not readily detectable by clinical or radiographic evaluation. Such parameters may be anatomic in nature, such as early spread to the cricoarytenoid joint or early spread through the conus elasticus, which are radiographically occult. This may help explain the observation noted by Fein et al that impaired vocal cord mobility was associated with a reduced likelihood of local control with radiation therapy (1). It is possible that the lack of such an anatomic correlation with relation to local control in our study may be attributable to a sampling error resulting from a smaller patient population; however, the volumetric analysis does not seem to be at issue.

No specific anatomic subsite, when involved by a tumor, was associated with a higher rate of local failure. Anterior commissure involvement by a T2 glottic lesion is therefore not a contraindication to treatment with definitive radiation therapy as previously reported (13, 14). All of the involvements of the anterior commissures in this series had no evidence of invasion of the laryngeal cartilage and were free of bulk disease at the anterior commissure extending into the low preepiglottic space; these factors can be confirmed with CT. Such more advanced anterior commissure cancers would likely be at a higher risk of treatment failure locally if treated with definitive radiation therapy. Failures of treatment in small-volume tumors may also be related to more biologically aggressive tumors, poor host resistance, or other tumor-host interactions, which are currently incompletely understood. There is mounting evidence, however, that treatment-related parameters such as dose per fraction and overall treatment time may also influence the chances of local control (15–18).

Although CT did not allow separation of patients with T2 glottic tumors into high- and low-risk groups, imaging plays an important role in the pretreatment evaluation of patients with clinical T2 lesions. CT has been helpful in identifying submucosal spread to the false cord paraglottic space, subglottic spread to the adjacent cricoid cartilage, and early spread through the cricothyroid membrane. These spread patterns potentially contraindicate treatment with classical vertical hemilaryngectomy. Failure of proper identification of such involvement by direct endoscopy may prevent complete surgical excision and result in treatment failure. Moreover, the occasional patient who is clinically T2 but has gross cartilage invasion (usually at the anterior commissure) can be identified with CT and, if desired, may be triaged to total or near-total laryngectomy rather than radiation therapy.

In conclusion, unlike supraglottic and T3 glottic tumors, CT does not allow stratification of patients with T2 glottic tumors treated with radiation therapy into groups at relatively high and low risk for failure based on volume or tumor scoring. CT confirms that these lesions are all very likely to be controlled by radiation therapy alone. The rate of local control (82% to 85%) is similar to that of favorable supraglottic

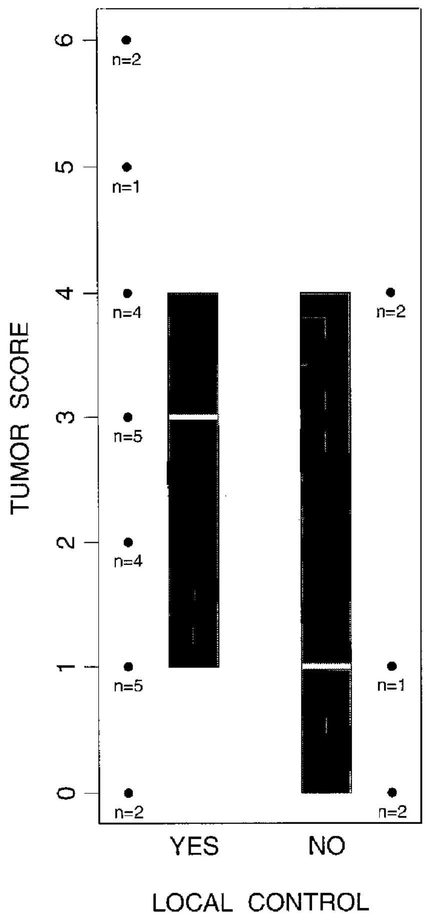


Fig 4. Distribution of tumor score by local control is depicted with a combination of scatter points and modified box plot. The *box* spans the range of tumor scores from the 25th to 75th percentiles. The *bar* within the box indicates the median tumor score. There was no significant difference in tumor score between patients whose tumors were locally controlled with radiation therapy and those patients for whom treatment failed (P = .377).

and T3 glottic lesions as defined by CT. In fact, the CT "profile" (volume and tumor score) of a T2 lesion is much the same as a favorable T3 lesion.

It seems there are factors that cause primary site failure that cannot be explained on the basis of pathoanatomic extent, tumor volume, or a combination of the two. This is likely because of more biologically aggressive tumors or tumor-host interactions, which are not fully understood. It is likely that biological markers will need to be identified to define better the small group of patients for whom treatment is likely to fail despite their having lesions that are favorable for cure on the basis of current clinical and diagnostic evaluation.

TABLE 2: Local control according to amount of subglottic extension on pretreatment CT (28 patients)

Subglottic Extension, mm	Local Control (%)	*P* Value
0–5	15/19 (79.0)	1.00
6–10	8/9 (88.9)	

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