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S. Çağlı, M. Öztürk, I. Yüce, K. Deniz and E. Güney

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**ORIGINAL
RESEARCH**

S. Çağlı
M. Öztürk
İ. Yüce
K. Deniz
E. Güney

The Value of Routine Clinical and Radiologic Studies in Predicting Neoplastic Invasion of Cricoarytenoid Units

BACKGROUND AND PURPOSE: Evaluation of the laryngeal cartilages is essential for the treatment strategy of patients with laryngeal carcinoma. Our aim was to assess the accuracy of preoperative clinical examinations and CT for preoperative evaluation.

MATERIALS AND METHODS: A prospective comparative study was performed at a university department on 30 patients with advanced laryngeal carcinomas. All patients were men and underwent total laryngectomy. The preoperative mobility of vocal folds was evaluated and classified as mobile, impaired, or fixed. CT was performed by using multidetector row CT. Cricoarytenoid units (CAUs) from the laryngectomy specimens were cut into sections. Histologic findings were compared with the clinical and radiologic findings.

RESULTS: The accuracy of combined clinical and CT staging in CAUs with normal mobility, impaired mobility, and absent mobility and negative CT findings was 96.5%, 50%, and 80%, respectively. These scores were 40%, 54.5%, and 83.3% for CAUs with normal mobility, impaired mobility, and absent mobility and positive CT findings, respectively.

CONCLUSIONS: Arytenoid mobility and >1 cartilage abnormality on CT were found to be reliable indicators of neoplastic cartilage invasion in patients with laryngeal carcinoma.

Laryngeal carcinoma is one of the most frequent malignancies of the head and neck region. The main goal in treating laryngeal squamous cell carcinoma is to control tumors locally while preserving the physiologic functions of speech and swallowing without permanent tracheostomy. Radiation therapy and partial laryngectomy can be curative for certain laryngeal tumors with preservation of the voice. This function-sparing operation requires at least 1 cricoarytenoid unit (CAU) to be preserved with clear margins. Although in the case of limited thyroid cartilage invasion some type of partial laryngectomy, such as subtotal laryngectomy with cricohyoidopexy, can still be a useful alternative, arytenoid and/or cricoid cartilage invasion indicates the necessity of extended partial laryngectomy, near-total laryngectomy, or total laryngectomy. The adjuvant use of combined chemotherapy and radiation therapy with salvage surgery seems a good alternative to near-total or total laryngectomy in the management of such cases. However, cricoid cartilage invasion generally dictates the necessity of total laryngectomy. It has been shown that radiation therapy is also not an appropriate treatment for both glottic and supraglottic laryngeal carcinomas with neoplastic cricoid cartilage invasion.^{1,2}

Because it is nearly impossible to obtain biopsy proof of cartilage invasion, evaluation of the laryngeal cartilages is mainly based on clinical, endoscopic, and radiologic evaluations. Preoperative indirect laryngoscopy, telescopic laryngoscopy, or fiberoptic laryngoscopy are routine in many clinics to evaluate the mobility of the arytenoids during phonation and

respiration, and they provide an accurate assessment of the surface extent of the tumor.

Cross-sectional radiologic imaging allows the evaluation of the deep extent of the tumor and its relationship to deep structures. In the detection of neoplastic cartilage invasion of arytenoid and cricoid cartilage, both CT and MR imaging have their own advantages and disadvantages. Although MR imaging is more sensitive than CT in the detection of neoplastic cartilage invasion of arytenoid and cricoid cartilage, for practical reasons CT is generally the preferred option.^{3,4} Several diagnostic CT signs, such as sclerosis of the cartilage, obliteration of the medullary cavity, irregular contour, erosion, cartilage blowout, and tumor on both sides of a cartilage, have been proposed as signs of cartilage invasion. Among these, only the presence of tumor on both sides of a cartilage has generally been accepted as a reliable sign of tumoral invasion, but this criterion becomes positive in only an advanced stage of the disease.⁵ Cartilage sclerosis has been one of the most common signs, and it is a commonly used CT criterion to predict tumor invasion of the arytenoid and cricoid cartilage. However, sclerotic changes in the laryngeal cartilage as a result of tumoral involvement are controversial.

To our knowledge, there are few available reports comparing the impact of clinical/endoscopic examination and CT in the pretherapeutic staging of laryngeal carcinoma, and none of these address the cricoarytenoid units (CAU). The aim of the present study was to assess the accuracy of routine and widespread use of studies such as endoscopy and CT, by comparing findings of each technique with histopathologic sections of total laryngectomy specimens. Pathologic findings were taken as the gold standard.

Materials and Methods

The study was prospectively performed between 2003 and 2007 and involved 30 patients with primary squamous cell carcinoma of the larynx who were treated with total laryngectomy.

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From the Departments of Otorhinolaryngology and Head and Neck Surgery (S.Ç., İ.Y., E.G.), Radiology (M.Ö.), and Pathology (K.D.), Erciyes University, Kayseri, Turkey.

Please address correspondence to Sedat Çağlı, MD, Erciyes University Medical Faculty, Department of Otolaryngology, Head & Neck Surgery, 38039 Talas-Kayseri, Turkey; e-mail: caglisdat@yahoo.com

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Fig 1. A, Sclerosis of the right arytenoid cartilage on an axial CT scan obtained at the glottic level (white arrow). B, Sclerosis of the cricoid cartilage on an axial CT scan obtained at the subglottic level (black arrow). Both were confirmed by histopathologic examination for neoplastic invasion (true-positive).

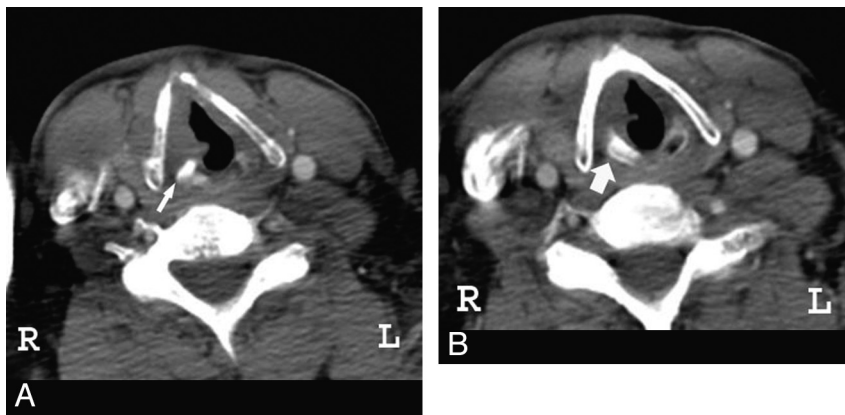


Fig 2. False-positive samples. A, Sclerosis of the right arytenoid cartilage on an axial CT scan obtained at the glottic level (thin arrow). B, Sclerosis of the cricoid cartilage on an axial CT scan obtained at the subglottic level (thick arrow).

Preoperative mobility of the vocal folds was evaluated by indirect laryngoscopy, telescopic laryngoscopy, or transnasal fiberoptic laryngoscopy and video documentation. Mobility was classified as mobile, impaired, or fixed. Primary lesions were staged according to the 2002 tumor-node-metastasis classification of the American Joint Committee on Cancer.⁶

All CT scans were obtained before direct laryngoscopy and biopsy. CT was performed by using a multidetector row CT scanner (Light-Speed 16; GE Healthcare, Milwaukee, Wis) and involved the acquisition of contiguous 1.25-mm transverse images that were reconstructed by using a soft-tissue algorithm and viewed by using both soft-tissue and bone window settings. Images were obtained with the patient in the supine position by using a detector configuration of 16×0.625 mm, pitch of 1.7, rotation time of 0.5 seconds, 240 mAs, and 120 kV. One hundred milliliters of intravenous nonionic contrast material was administered at a flow of 3.0 mL/s. Postprocessing and multiplanar reformatting and interpretation were performed on a dedicated workstation.

All scans were evaluated by a radiologist experienced in cross-sectional studies of the head and neck area. Cartilage sclerosis was defined as thickening of the cortical margin or increased medullary attenuation. Asymmetric sclerosis was decided by comparing 1 arytenoid to the other or 1 side of the cricoid cartilage with the other. We did not specifically address other findings that are highly suggestive of cartilage invasion such as lysis, cartilage explosion, and visible tumor on both sides of the cartilage (Figs 1 and 2).

Surgical resections were performed 7–10 days after the last imaging study. A total of 30 total laryngectomy specimens with laryngeal

carcinoma were subjected to serial section study. First, samples for detection of the surgical borders were taken. Then specimens were opened along the vertical line at the interarytenoid junction, and both arytenoids and cricoarytenoid joints were removed separately (Fig 3). CAU specimens were fixed with formalin and embedded in paraffin, and 5- μ m sections were stained with hematoxylin-eosin (H&E). The histologic sections were examined under light microscope by a pathologist familiar with laryngeal neoplasms but without knowledge of the clinical, radiologic, or surgical findings (Fig 4).

All statistical analyses were performed by using the Statistical Package for the Social Sciences for Windows (Version 15; SPSS, Chicago, Ill). The frequency of mobile, impaired, and fixed vocal folds was compared with the frequency of histopathologic involvement by using the χ^2 and Fisher exact tests. A *P* value < .05 was considered statistically significant. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated for cartilage sclerosis on CT. The agreement of CT and histopathologic findings was assessed with the Cohen κ statistic. The agreement was determined with κ values as follows: 0–.20, very poor; 0.21–0.40, poor; 0.41–0.60, fair; 0.61–0.80, good; and 0.81–1.00, excellent. General log-linear analysis with a multinomial model was used to compare arytenoid mobility with CT findings in patients with positive pathologic findings.

Results

There were 30 men with a mean age of 59 years. All patients had squamous cell carcinoma, and all patients underwent total

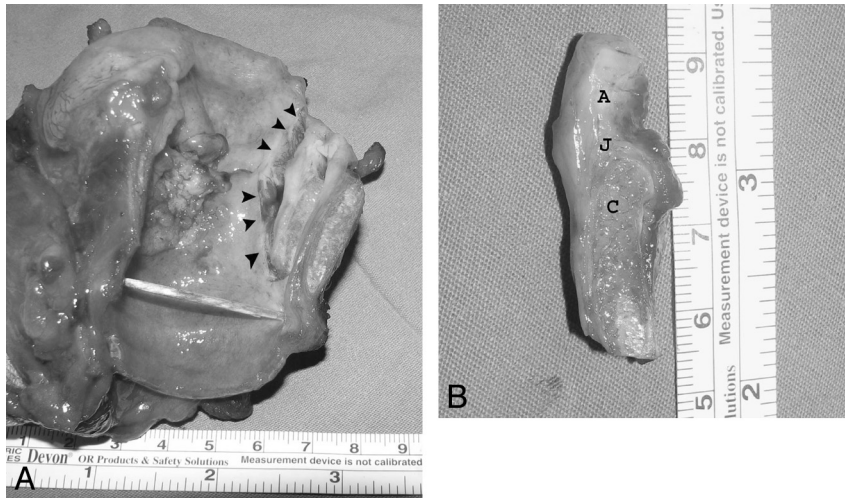


Fig 3. Opening the total laryngectomy specimen along the vertical line at the interarytenoid junction and sampling of the cricoarytenoid unit. *A*, Incisions (*arrowheads*). *B*, Macroscopic appearance of the CAU. *A* indicates arytenoid cartilage; *J*, joint; *C*, cricoid cartilage.

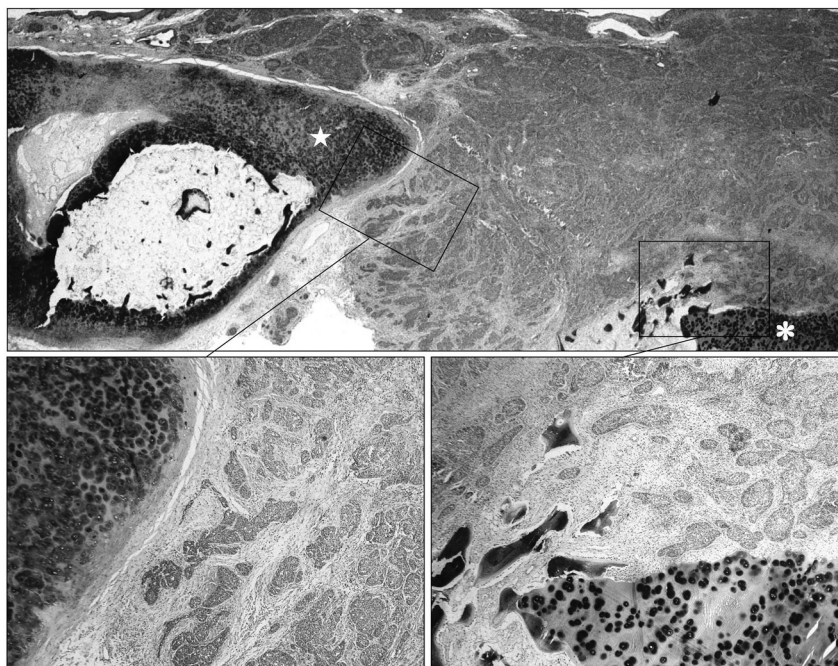


Fig 4. Photomicrograph shows squamous cell carcinoma infiltrating the cricoid cartilage (*asterisk*), cricoarytenoid joint, and arytenoid cartilage (*star*). (H&E, original magnification $\times 4$, $\times 100$, $\times 100$).

laryngectomy. Fourteen of the primary tumors were staged as T3 and 16 as T4.

In a total of 60 specimens, the CAUs were invaded in 20 specimens. Sixteen of the specimens had arytenoid, cricoid, and/or cricoarytenoid joint (CAJ) invasions. There was no isolated cricoid cartilage invasion; isolated arytenoid cartilage and CAJ invasions were found only in 2 specimens.

Clinical and Endoscopic Findings

On the basis of indirect or fiberoptic laryngoscopy, arytenoid mobility was impaired in 15 and absent in 11 of the CAUs. Although only 3 CAUs were found to show neoplastic invasion in 34 clinically mobile CAUs (8.8%), 8 of the 15 units (53.3%) with impaired mobility and 9 of the 11 fixed units

Table 1: Pathologic results according to arytenoid mobility

| Mobility | Pathologically Positive | Pathologically Negative | Total |
|----------|-------------------------|-------------------------|-------|
| Mobile | 3 | 31 | 34 |
| Impaired | 8 | 7 | 15 |
| Fixed | 9 | 2 | 11 |
| Total | 20 | 40 | 60 |

(81.8%) were found to have neoplastic invasion ($P = .000$) (Table 1).

CT Findings

Thirty-eight of the 60 CAUs were normal on CT, and 22 of the 60 CAUs showed cartilage sclerosis on CT. Among the 22 CT-

Table 2: Pathologic results according to CT findings

| CT Findings | Pathologically Positive | Pathologically Negative | Total |
|-------------|-------------------------|-------------------------|-------|
| CT positive | 13 | 9 | 22 |
| CT negative | 7 | 31 | 38 |
| Total | 20 | 40 | 60 |

Table 3: CT findings according to arytenoid mobility in pathologically positive CAUs

| | Pathologically Positive | | Total |
|---------------------------|-------------------------|--------------|---------------|
| | CT Positive | CT Negative | |
| Mobile (<i>n</i> = 34) | 2/5 (40%) | 1/29 (3.4%) | 3/34 (8.8%) |
| Impaired (<i>n</i> = 15) | 6/11 (54.5%) | 2/4 (50%) | 8/15 (53.3%) |
| Fixed (<i>n</i> = 11) | 5/6 (83.3%) | 4/5 (80%) | 9/11 (81.8%) |
| Total | 13/22 (59%) | 7/38 (18.4%) | 20/60 (33.3%) |

Note:—CAUs indicate cricoarytenoid units.

positive CAUs, 14 had isolated asymmetric arytenoid sclerosis, 2 had isolated cricoid sclerosis, and 6 had both arytenoid and cricoid sclerosis. Thirteen CAUs with cartilage sclerosis (59%) and 7 CAUs with normal findings (18.4%) were found to show neoplastic invasion on histopathologic examinations (κ value, 0.41; $P = .001$) (Table 2). CT findings were true-positive in 13, true-negative in 31, false-positive in 9, and false-negative in 7 CAUs, for a 73.3% accuracy. Positive and negative predictive values were 59% and 81.6%, respectively. The sensitivity of cartilage sclerosis was 65%, and the specificity was 77.5%. None of the 60 units showed isolated CAJ abnormality. Seven of 14 (50%) isolated sclerotic arytenoid cartilages and 2 (100%) isolated sclerotic cricoid cartilages showed neoplastic invasion on histopathologic examination. Four of 6 (66.6%) with sclerosis of multiple cartilages on CT demonstrated neoplastic invasion.

Combined Clinical and CT Findings

The accuracy of combined clinical and CT staging in CAUs with normal mobility, impaired mobility, and absent mobility and negative CT findings was 96.6%, 50%, and 80%, respectively. These scores were 40%, 54.5%, and 83.3% for CAUs with normal mobility, impaired mobility, and absent mobility and positive CT findings, respectively ($P < .001$) (Table 3).

Discussion

In preserving the functions of the larynx while treating cancer, the fundamental problem for the clinician is to decide whether the tumor is suitable for conservative surgery. It is often suggested that cartilage involvement precludes voice-sparing partial laryngectomy and is also a contraindication to radiation treatment. Although the invasion of thyroid cartilage does not preclude the conservative functional surgeries, arytenoid and/or cricoid cartilage invasion requires more extensive surgeries. Neoplastic invasion of the cricoid cartilage is more important. Cricoid cartilage invasion generally reduces both the chance of voice-preserving surgery^{7,8} and the chance of cure with radiation therapy.^{1,2} Thus, the accuracy of pretherapeutic staging carries paramount importance in the treatment planning of laryngeal cancer. In routine practice, this is generally provided by endoscopic evaluations and CT imaging.

Preoperative indirect and direct laryngoscopies can assess

the cartilage invasion. Arytenoid immobility is one of the most important clinical signs of CAU involvement by cancer, and fixation of this cartilage is generally accepted as a contraindication of voice-sparing conservative laryngeal surgery. Sparano et al⁹ suggested that arytenoid fixation much more significantly correlated with cricoid cartilage invasion than true vocal cord fixation.

Our study showed that mobile arytenoid cartilage is a good predictive sign of tumor-free CAUs, with a 91.2% accuracy. Fixation of the arytenoids is also a reliable indicator of tumor involvement in these structures, having an 81.8% accuracy: A grossly invasive tumor with fixation of the larynx is considered to have invaded the cartilage.

Impairment of the arytenoid movement did not correlate well with histopathologic invasion. We think that false-positive and -negative findings of clinical examinations may be due to either the experience of the clinician or the weight effect of the tumor. The weight may cause impairment in the mobility of the arytenoid without involvement directly of the CAU and creates the false impairment of arytenoid movement. In this situation, the top of the arytenoid is immobile while its base, which cannot be seen with indirect laryngoscopy, remains mobile.¹⁰ On the other hand, impairment may occur without cartilage invasion.

Although clinical evaluation and biopsy of a laryngeal lesion at endoscopy is excellent for documenting the extent of mucosal spread, it is not very accurate in determining the depth of tumor invasion.^{11,12} Therefore, the clinician relies on modern radiologic assessment of the tumor, which is generally in the form of CT scans. CT has become an important radiologic adjunct in the pretherapeutic work-up of laryngeal cancer.⁴ There is a long-standing debate about the significance of cartilage abnormalities seen on pretherapeutic imaging studies in patients with laryngeal cancer. Tumor on both sides or the extralaryngeal side of the cartilage, which is usually present in advanced cases, is generally accepted as a specific radiologic sign of cartilage invasion and has a reported specificity of 95%.¹³ Other radiologic signs used to predict early cartilage invasion include cartilage sclerosis, intramedullary cartilaginous mass, cartilaginous explosion, cartilage lysis, and cartilage bowing.¹⁴⁻¹⁷ Sclerotic changes in the laryngeal cartilage as a result of tumoral involvement are controversial. The ability of CT to detect neoplastic invasion of laryngeal cartilage varies widely, with reported sensitivities of 46%–66% and specificities of 84%–94%.^{3,13,14,17-19}

Investigators have tried to use MR imaging to improve the accuracy of detecting early neoplastic cartilage invasion. Castelijns et al¹⁸ found that the specificity of CT and MR imaging in the detection of all laryngeal cartilages was approximately equal, 91% and 88%, respectively. Overall, the accuracy of both methods is similar.⁷ MR imaging also has the disadvantage of poor specificity, motion artifacts in patients with chronic respiratory disease that commonly accompanies laryngeal cancer, and limited availability.^{15,20} Difficulties in distinguishing neoplastic invasion from inflammatory involvement of the laryngeal cartilages reduces specificity. More recently, Becker et al²¹ showed that new diagnostic criteria, based on the signal-intensity behavior of cartilage on T2-weighted and contrast-enhanced T1-weighted images, enable

improved differentiation of neoplastic cartilage invasion from peritumoral inflammation.

In our study, the accuracy of cartilage sclerosis on CT alone was found to be 73.3%. However, the positive predictive value of CT (59%) was lower than the negative predictive value (81.6%). The limitation of CT in determining cartilage invasion may be related to the irregular mix of calcified, ossified, and noncalcified cartilage.^{3,18,22} In a study analyzing 100 CT examinations of patients of different ages and no history of radiation therapy to the neck or laryngeal cancer, a sclerotic arytenoid cartilage was observed in 16% of patients.²³ In concordance with the related literature, in our study, the positive predictive value of isolated arytenoid sclerosis on CT was only 50%. We think that asymmetric sclerosis of the arytenoid cartilages in patients with laryngeal squamous cell carcinoma is a frequent feature, and isolated arytenoid cartilage sclerosis alone is not a reliable marker of neoplastic cartilage invasion due to its low sensitivity and specificity. However, the positive predictive rate increased to 75% in the case of asymmetric cricoid cartilage sclerosis associated with arytenoid sclerosis. This finding can be important because some studies have indicated that arytenoid and adjacent cricoid cartilage sclerosis may be a risk factor for local recurrence and poor outcome.² Isolated cricoid cartilage sclerosis was found to be the most reliable indicator of cartilage invasion (100%). Laryngeal cartilage sclerosis, except for cricoid sclerosis, was not a useful early radiologic sign of neoplastic cartilage invasion.¹¹

Conclusions

Mobility of the arytenoid is the most useful indicator of tumor-free CAUs. The highest accuracy rate is obtained when mobile arytenoid and negative CT findings are associated (96.6%). Asymmetric cricoid cartilage sclerosis appears to be a reliable indicator of cartilage invasion (75%–100%). Isolated arytenoid cartilage sclerosis on CT does not always imply neoplastic cartilage invasion and should not be used as a sole criterion for prediction. Pretreatment studies of patients with impaired arytenoid movements and/or isolated arytenoid sclerosis should be supplemented with other advanced imaging techniques.

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