Neoplastic Invasion of Laryngeal Cartilage: Reassessment of Criteria for Diagnosis at MR Imaging[1]

Minerva Becker, MD
Peter Zbären, MD
Jan Walther Casselman, MD
Romain Kohler, MD
Pavel Dulguerov, MD
Christoph D. Becker, MD

Purpose: To evaluate whether proposed diagnostic criteria applied to magnetic resonance (MR) images of patients with laryngeal and hypopharyngeal carcinoma may be used to distinguish neoplastic from inflammatory involvement of the laryngeal cartilages.

Materials and Methods: The radiologic and histopathologic data in 121 consecutive patients with primary squamous cell carcinoma of the larynx ($n = 63$) or hypopharynx ($n = 58$) who underwent MR imaging before laryngectomy formed the basis of this retrospective study. Patient consent for retrospective chart review was waived by the institutional review board. All laryngectomy specimens were processed with a dedicated histopathologic whole-organ slice technique. MR images were evaluated by two readers according to established ("old") and proposed ("new") diagnostic criteria on the basis of the signal intensity behavior of cartilage on T2-weighted images and contrast material–enhanced T1-weighted images compared with that of the adjacent tumor. Specifically, with the new criteria, T2-weighted or postcontrast T1-weighted cartilage signal intensity greater than that of the adjacent tumor was considered to indicate inflammation, and signal intensity similar to that of the adjacent tumor was considered to indicate neoplastic invasion. The results of the MR image interpretation were compared with the histologic reference standard.

Results: The area under the receiver operating characteristic curve for the new criteria (0.94) was nominally but significantly larger than that for the old criteria (0.92) ($P = .01$). Overall specificity was significantly improved (82% for new vs 74% for old criteria, $P < .001$) and was greatest for the thyroid cartilage (75% for new vs 54% for old criteria, $P < .001$) with the new criteria. The sensitivities of the established and the proposed criteria were identical.

Conclusion: The proposed MR imaging criteria enable improved differentiation of neoplastic cartilage invasion from peritumoral inflammation.

[1] From the Departments of Radiology (M.B., R.K., C.D.B.) and Otorhinolaryngology (P.D.), Geneva University Hospital, Hôpitaux Universitaires de Genève, Rue Micheli-du-Crest 24, CH-1211 Geneva 14, Switzerland; Department of Radiology, AZ Sint Jan Hospital, Bruges, Belgium (J.W.C.); and Department of Otorhinolaryngology, Head and Neck Surgery, Insel Hospital, Berne, Switzerland (P.Z.). Received December 21, 2007; revision requested February 20, 2008; revision received March 14; accepted May 5; final version accepted May 15. **Address correspondence to** M.B. (e-mail: *minerva.becker@hcuge.ch*).

Cartilage invasion in laryngeal and hypopharyngeal cancer affects classification according to the American Joint Committee on Cancer and the Union Internationale Contre le Cancer and has important implications for treatment and prognosis (1–7). Although the correct prediction of cartilage invasion affects the type of surgery (various types of partial voice-preserving laryngectomy vs total laryngectomy), the presence of neoplastic cartilage invasion may also affect the response to radiation therapy, leading to a higher rate of tumor recurrence (2,5–11).

Several investigators (12–15) have shown that magnetic resonance (MR) imaging has a high sensitivity and a high negative predictive value for the detection of neoplastic cartilage invasion, therefore allowing exclusion of cartilage invasion quite reliably. However, the specificity and positive predictive value obtained with currently accepted MR imaging criteria remain unsatisfactory. The main reason for this drawback is that peritumoral inflammation may mimic neoplastic invasion on both T2-weighted and contrast material–enhanced T1-weighted images, especially in the thyroid cartilage (2–4,12), thereby leading to overstaging and possibly overtreatment of disease.

On the basis of our clinical experience, we hypothesized that in some cases the laryngeal cartilages display higher signal intensity than the soft-tissue component of the tumor on T2-weighted images and that this higher signal intensity within the cartilage tends to correspond to peritumoral inflammation at histopathologic examination, whereas areas of signal intensity within the laryngeal cartilages that are similar to that of the tumor correspond to intracartilaginous tumor tissue. Likewise, we hypothesized that peritumoral inflammatory tissue within the laryngeal cartilages shows stronger enhancement than adjacent tumor. On the basis of these observations, we proposed a modified set of diagnostic criteria for neoplastic cartilage invasion. Our hypothesis was that these new criteria could be used to distinguish neoplastic cartilage invasion from peritumoral inflammation extending into the cartilaginous tissue.

The purpose of this study was therefore to evaluate whether the proposed diagnostic criteria applied to MR images in patients with laryngeal and hypopharyngeal carcinoma may be used to distinguish neoplastic from inflammatory involvement of the laryngeal cartilages.

Advances in Knowledge

- In assessing potential neoplastic infiltration of laryngeal cartilage at MR imaging, the T2-weighted and gadolinium-enhanced T1-weighted signal intensity should be compared with the signal intensity of the adjacent tumor on the corresponding sequences: If the cartilage displays higher signal intensity than tumor, a diagnosis of peritumoral inflammation within the cartilage is suggested; if, however, the cartilage displays a similar signal intensity to tumor, neoplastic cartilage invasion is suggested.
- The use of the diagnostic criteria proposed in this study significantly improves the specificity of MR imaging for the detection of cartilage invasion ($P < .001$) without affecting its high sensitivity; distinction between tumor and peritumoral inflammatory tissue might therefore be made more accurately.

Materials and Methods

Patients and Tumor Characteristics

The study was based on the retrospective analysis of MR images and histopathologic data in a series of 121 consecutive patients (median age, 63 years; age range, 36–86 years) with primary squamous cell carcinoma of the larynx ($n = 63$) or hypopharynx ($n = 58$) who had undergone MR imaging prior to surgery and for whom results of dedicated whole-organ cross-sectional histopathologic examination of the resected specimen were available. Patient consent for retrospective chart review was waived by the institutional review boards of the University Hospitals of Berne and Geneva. Forty-six patients underwent total laryngectomy, 43 patients underwent pharyngolaryngectomy, eight patients underwent circular pharyngolaryngectomy, 17 patients underwent partial laryngectomy, and seven patients underwent partial pharyngolaryngectomy. According to the guidelines of the Union Internationale Contre le Cancer (1) for postsurgical or pathologic classification (pT staging), the 63 laryngeal tumors were classified as pT1 ($n = 4$), pT2 ($n = 8$), pT3 ($n = 29$), and pT4 ($n = 22$), and the 58 hypopharyngeal tumors were classified as pT1 ($n = 3$), pT2 ($n = 11$), pT3 ($n = 11$), and pT4 ($n = 33$).

Implication for Patient Care

- On the basis of our preliminary experience, these proposed diagnostic MR imaging criteria may facilitate the distinction between patients with and those without neoplastic cartilage invasion, a distinction that may be useful for treatment planning.

MR Imaging Protocol

All MR imaging studies that were available for retrospective chart review had been obtained at 1.5 T and

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Abbreviations:
A_z = area under the ROC curve
ROC = receiver operating characteristic

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Guarantors of integrity of entire study, M.B., C.D.B.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, M.B., R.K., P.D.; clinical studies, M.B., P.Z., J.W.C., P.D.; statistical analysis, M.B., XXX; and manuscript editing, M.B., R.K., C.D.B.

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See also the editorial by Curtin in this issue.

included a sagittal T1-weighted localizer image (repetition time msec/echo time msec, 8–30/5), axial T2-weighted fast spin-echo images (4450–5600/80–100), axial T1-weighted spin-echo images (320–480/10–12), and T1-weighted spin-echo images (320–480/10–12) obtained after intravenous administration of 0.1 mmol/L gadolinium chelate per kilogram of body weight. Fat-saturated images were not available for most patients. For all sequences, the section thickness was 3–4 mm, with a 0–0.4-mm intersection gap. The field of view was 200 × 200 mm, with a 256–512 × 256–512 acquisition matrix.

Histologic Evaluation

Whole-organ histologic slices parallel to the plane of the axial MR images were available for retrospective review. These slices had been obtained every 3–4 mm through the entire surgical specimen and had been processed according to a technique described in other publications (8,12–18).

At histopathologic examination, the thyroid, cricoid, and arytenoid cartilages were considered to be invaded if the perichondrium was invaded, if there was intracartilaginous tumor spread with preservation of the outer perichondrium, or if there was major cartilage destruction with tumor in the extralaryngeal soft tissues. In addition, all cartilages were evaluated with respect to the presence or absence of inflammatory changes (peritumoral inflammation), new bone formation, erythropoietic bone marrow, and fibrosis. All histopathologic slices were retrospectively reviewed by a pathologist with 25 years of experience, and the MR imaging findings were then correlated with histopathologic findings at the respective anatomic levels.

Diagnostic Criteria

The MR imaging criteria that were used for the diagnosis of neoplastic invasion of laryngeal cartilages in this study are defined below.

In a first step, all laryngeal cartilages were evaluated by using the criteria that have been established and used by previous investigators (2,3,5–7,9,12–15). The established ("old") criteria for neoplastic invasion of ossified and nonossified hyaline laryngeal cartilages are summarized in Table 1.

With our proposed ("new") diagnostic criteria for distinguishing tumor invasion from peritumoral inflammation, the signal intensity of the cartilage is compared with the signal intensity of the adjacent tumor mass outside the cartilage, which is used as an internal reference standard. If the cartilage has a similar signal intensity to the adjacent tumor mass on T2-weighted images, or if—after injection of a gadolinium chelate—a similar enhancement is seen in the cartilage as in the adjacent soft-tissue component of the tumor, the cartilage is considered to be invaded by tumor. However, if the cartilage has a higher signal intensity than the adjacent tumor on T2-weighted images and if a stronger enhancement is present after injection of gadolinium chelates, the abnormal signal intensity behavior of the cartilage is regarded as indicative of peritumoral inflammation without associated tumor invasion. The difference between the signal intensities of the tumor adjacent to the cartilage and the cartilage itself was assessed visually without specific region of interest measurements, as the signal intensity of the soft-tissue component of the tumor was used as an internal reference standard at each corresponding anatomic level. These proposed criteria are also summarized in Table 1.

Evaluation of Data

The MR images were retrospectively reviewed and evaluated by two head and neck radiologists (M.B. and J.W.C.,

Table 1

Established ("Old") and Proposed ("New") MR Imaging Criteria for Detection of Neoplastic Invasion of Laryngeal Cartilages

	Signal Intensity or Enhancement	
Tissue and Sequence	Ossified Hyaline Cartilage	Nonossified Hyaline Cartilage
Normal cartilage		
T1-weighted spin echo	High (fatty marrow)	Low
T2-weighted fast spin echo	High (fatty marrow)	Low
Gadolinium-enhanced T1-weighted spin echo	No enhancement	No enhancement
Cartilaginous invasion by tumor according to old criteria		
T1-weighted spin echo	Low	Low
T2-weighted fast spin echo	Intermediate or high	Intermediate or high
Gadolinium-enhanced T1-weighted spin echo	Any enhancement	Any enhancement
Cartilaginous invasion by tumor according to new criteria*		
T1-weighted spin echo	Low	Low
T2-weighted fast spin echo	Similar to that of tumor	Similar to that of tumor
Gadolinium-enhanced T1-weighted spin echo	Similar enhancement to tumor	Similar enhancement to tumor
Cartilaginous inflammation according to new criteria*		
T1-weighted spin echo	Low	Low
T2-weighted fast spin echo	Higher than that of tumor	Higher than tumor
Gadolinium-enhanced T1-weighted spin echo	Greater enhancement than tumor	Greater enhancement than tumor

Note.—Established criteria are described in references 2, 3, 5–7, 9, and 12–15.

* Distinction between tumor and peritumoral inflammation was made on the basis of visual assessment of the different signal intensities at each corresponding anatomic level by using the signal intensity of the soft-tissue component of the tumor as an internal reference standard.

with 15 and 20 years of experience, respectively) in consensus according to the diagnostic criteria listed in Table 1. No clinical information was available to the reviewers at the time of image interpretation, and they were blinded to the identity of the patients and to the results of histopathologic analysis. In a first step, they read all MR images and evaluated each of the laryngeal cartilages (thyroid, cricoid, and arytenoid) by using a combination of T1- and T2-weighted images according to the established criteria ("T1/T2 old") and according to the new criteria ("T1/T2 new"). In a second step, they read all MR images by using a combination of nonenhanced and gadolinium-enhanced T1-weighted sequences according to the established criteria ("T1/T1 + Gd old") and according to the new criteria ("T1/T1 + Gd new"). To avoid interpretation bias, the time interval between each of the four readings was at least 6 months. A five-point scale for receiver operating characteristic (ROC) analysis was used for each combination of criteria as follows: a score of 1 indicated definitely negative; a score of 2, probably negative; a score of 3, possibly positive; a score of 4, probably positive; and a score of 5, definitely positive for neoplastic invasion.

Table 2

MR Imaging Results for Detection of Neoplastic Invasion of Laryngeal Cartilages with Different Combinations of Diagnostic Criteria

Cartilage and Result	T1/T2 Old	T1/T2 New	T1/T1 + Gd Old	T1/T1 + Gd New
Thyroid (n = 121)				
No. of true-positive findings	47	47	47	47
No. of false-positive findings	33	18	38	25
No. of true-negative findings	39	54	34	47
No. of false-negative findings	2	2	2	2
Sensitivity (%)	96 (47/49)	96 (47/49)	96 (47/49)	96 (47/49)
Specificity (%)	54 (39/72)	75 (54/72)	47 (34/72)	65 (47/72)
PPV (%)	59 (47/80)	72 (47/65)	55 (47/85)	65 (47/72)
NPV (%)	95 (39/41)	96 (54/56)	94 (34/36)	96 (47/49)
Cricoid (n = 103)				
No. of true-positive findings	25	25	25	25
No. of false-positive findings	20	17	23	17
No. of true-negative findings	57	60	54	60
No. of false-negative findings	1	1	1	1
Sensitivity (%)	96 (25/26)	96 (25/26)	96 (25/26)	96 (25/26)
Specificity (%)	74 (57/77)	78 (60/77)	70 (54/77)	78 (60/77)
PPV (%)	56 (25/45)	60 (25/42)	52 (25/48)	60 (25/42)
NPV (%)	98 (57/58)	98 (60/61)	98 (54/55)	98 (60/61)
Arytenoid (n = 210)				
No. of true-positive findings	23	23	23	22
No. of false-positive findings	34	23	39	26
No. of true-negative findings	148	159	143	156
No. of false-negative findings	5	5	5	6
Sensitivity (%)	82 (23/28)	82 (23/28)	82 (23/28)	79 (22/28)
Specificity (%)	81 (148/182)	87 (159/182)	79 (143/182)	86 (156/182)
PPV (%)	40 (23/57)	50 (23/46)	37 (23/62)	46 (22/48)
NPV (%)	99 (148/149)	97 (159/164)	97 (143/148)	96 (156/162)
All cartilages (n = 434)				
No. of true-positive findings	95	95	95	94
No. of false-positive findings	87	58	100	68
No. of true-negative findings	244	273	231	263
No. of false-negative findings	8	8	8	9
Sensitivity (%)	92 (95/103)	92 (95/103)	92 (95/103)	91 (94/103)
Specificity (%)	74 (244/331)	82 (273/331)	70 (231/331)	79 (263/331)
PPV (%)	52 (95/182)	62 (95/153)	49 (95/195)	58 (94/162)
NPV (%)	97 (244/252)	97 (273/281)	97 (231/239)	97 (263/272)

Note.—Numbers in parentheses were used to calculate the percentages. NPV = negative predictive value, PPV = positive predictive value.

Statistical Analysis

MR imaging data were analyzed statistically in two ways: with sensitivity, specificity, positive predictive value, and negative predictive value tables and with ROC curves. This statistical approach was based on a review of the literature (12,13,19–23). For the calculation of sensitivity, specificity, positive predictive value, and negative predictive value, scores of 5 (definitely positive) and 4 (probably positive) were combined with scores of 3, which were considered as possibly indicating neoplastic invasion. We chose to use a confidence level of 3 because at our institution in a given clinical situation, "possibly positive" would be more likely to be considered a positive finding than a negative finding. For comparison of the different pulse sequence combinations in the thyroid and cricoid cartilages, the McNemar test on sensitivity, specificity, and accuracy was performed by using software (StatXact, version 2.01 for UNIX; Cytel Software, Cambridge, Mass) (17). For the same comparisons in the arytenoid cartilage and in all cartilages together, a generalized linear mixed model was applied to take into account the correlation between multiple cartilages in the same patient by using software (SAS, version 9.1 for Windows; SAS Institute, Cary, NC).

A computer program (ROCKIT, beta version 0.9.1 for Windows 95; Charles E. Metz, PhD, Department of Radiology, University of Chicago, Chicago, Ill) (20) was used to calculate the binormal ROC model parameters for each combination of MR imaging pulse sequences and to compute the ROC curves and the areas under the ROC curves (A_z values). The index A_z is generally accepted as the best measure of accuracy for a diagnostic mo-

Figure 1

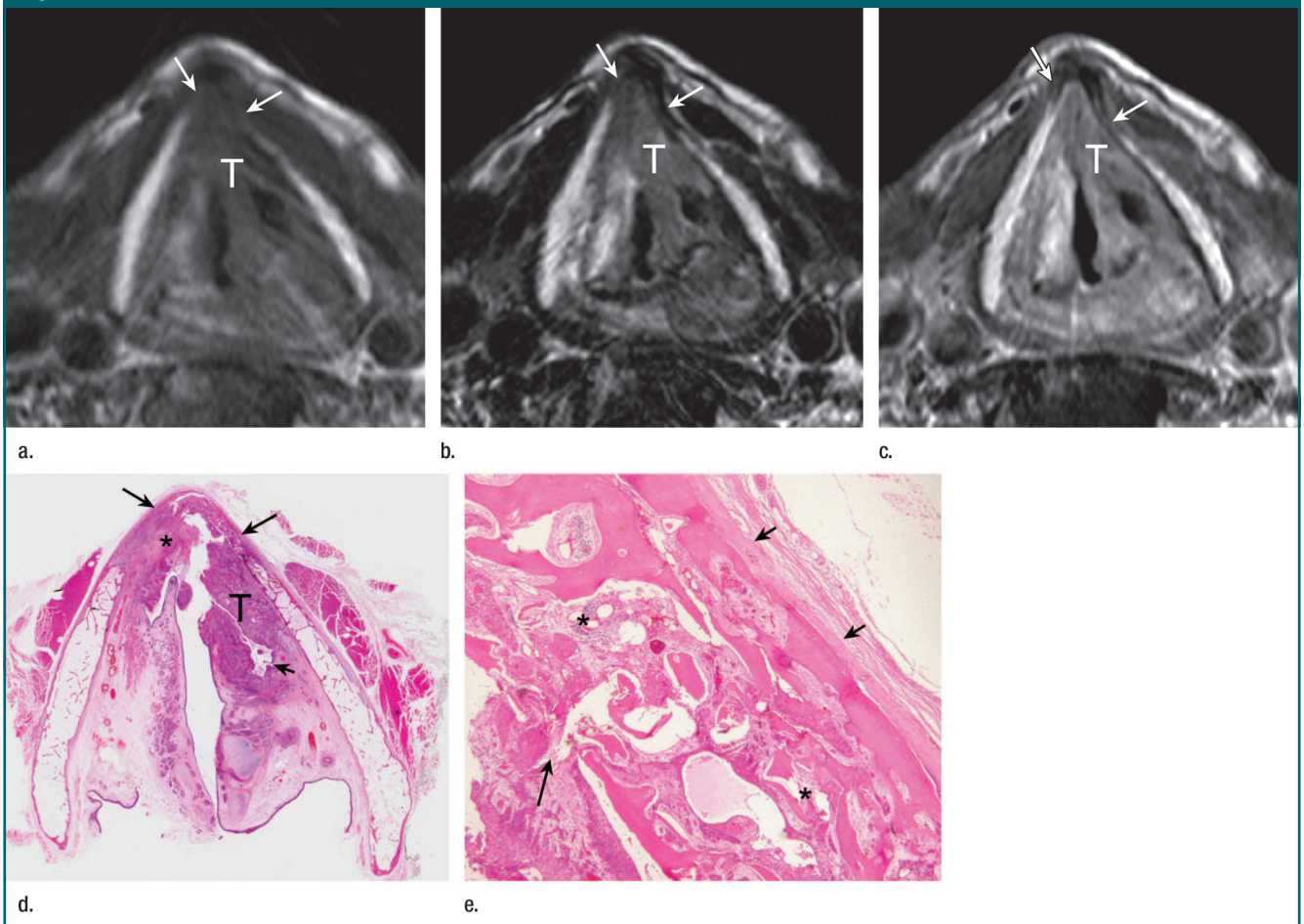

Figure 1: Axial MR imaging findings true-positive for neoplastic invasion of thyroid cartilage according to old and new diagnostic criteria. **(a)** T1-weighted MR image (460/12) obtained at supraglottic level shows left-sided laryngeal tumor *(T)* with intermediate to low signal intensity. Adjacent anterior right and left thyroid lamina also show an area of intermediate to low signal intensity (arrows). **(b)** T2-weighted fast spin-echo MR image (5668/100) obtained at same level as **a** shows that the tumor *(T)* has intermediately high signal intensity, whereas adjacent thyroid cartilage (arrows) has similar signal intensity. **(c)** T1-weighted MR image (460/12) obtained after intravenous administration of contrast material shows enhancement of the tumor mass *(T)* and similar enhancement of the adjacent thyroid lamina (arrows). This suggests—according to the old and the new MR imaging criteria—that the thyroid cartilage is invaded by tumor anteriorly. **(d)** Corresponding axial slice from surgical specimen at same level confirms that anterior thyroid cartilage is invaded by tumor (long arrows). The tumor *(T)* arises from the left laryngeal ventricle (short arrow) and extends into the contralateral false cord (*). (Hematoxylin-eosin stain.) **(e)** Detail in anterior left thyroid lamina (enlargement of area in **d**) shows destruction of inner perichondrium (long arrow) and invasion of marrow space by tumor cells (*). Note that the outer perichondrium (short arrows) is still intact. (Hematoxylin-eosin stain; original magnification, ×25.)

dality. ROCKIT was also used to test the difference between the ROC areas for the two sets of criteria, taking into account the correlation between readings with two methods of the same image. $P < .05$ was considered to indicate a significant difference.

Results

Correlation between MR imaging and histopathologic findings was available for 121 specimens (46 total laryngectomy specimens, 43 pharyngolaryngectomy specimens, eight circular pharyngolaryngectomy specimens, 17 partial laryngectomy specimens, and seven partial pharyngolaryngectomy specimens). This corresponded to a total of 434 analyzed cartilages (121 thyroid cartilages, 103 cricoid cartilages, and 210 arytenoid cartilages) in which results of complete histopathologic work-up were available. Histologically, tumor was present in 49 thyroid cartilages, 26 cricoid cartilages, and 28 arytenoid cartilages and was absent in 72 thyroid cartilages, 77 cricoid cartilages, and 182 arytenoid cartilages. This resulted in an overall prevalence of intracartilaginous tumor of 24%. Various degrees of peritumoral inflammatory changes were found both in the invaded and in the noninvaded laryngeal cartilages surrounding the actual tumor borders.

The overall prevalence of intracartilaginous inflammation without associated intracartilaginous tumor was 41%.

Correlation between MR Imaging and Histopathologic Results

MR imaging results for the detection of neoplastic infiltration of the thyroid cartilage, cricoid cartilage, and arytenoid cartilage and for all cartilages together for scores of 5 (definitely positive), 4 (probably positive), and 3 (possibly positive) are summarized in Table 2.

For all criteria and in all cartilages, the true-positive MR imaging assessments corresponded to major or minor neoplastic invasion of the cartilage (Fig 1), and the false-negative MR imaging assessments were caused by microscopic perichondrial invasion or (only rarely) by minor intracartilaginous tumor spread (in two arytenoid cartilages). All false-positive MR imaging assessments made by using either the old (Figs 2, 3) or the new diagnostic criteria were caused by various degrees of inflammatory changes within the cartilages, including plasma cell infiltrates, lymph follicles, microscopic areas of fibrosis, bone and cartilage remodeling, and increased vascularization and edema, but no evidence of invasion. The true-negative MR imaging assessments with both the old and the new criteria corresponded to noninvaded cartilages

Figure 2

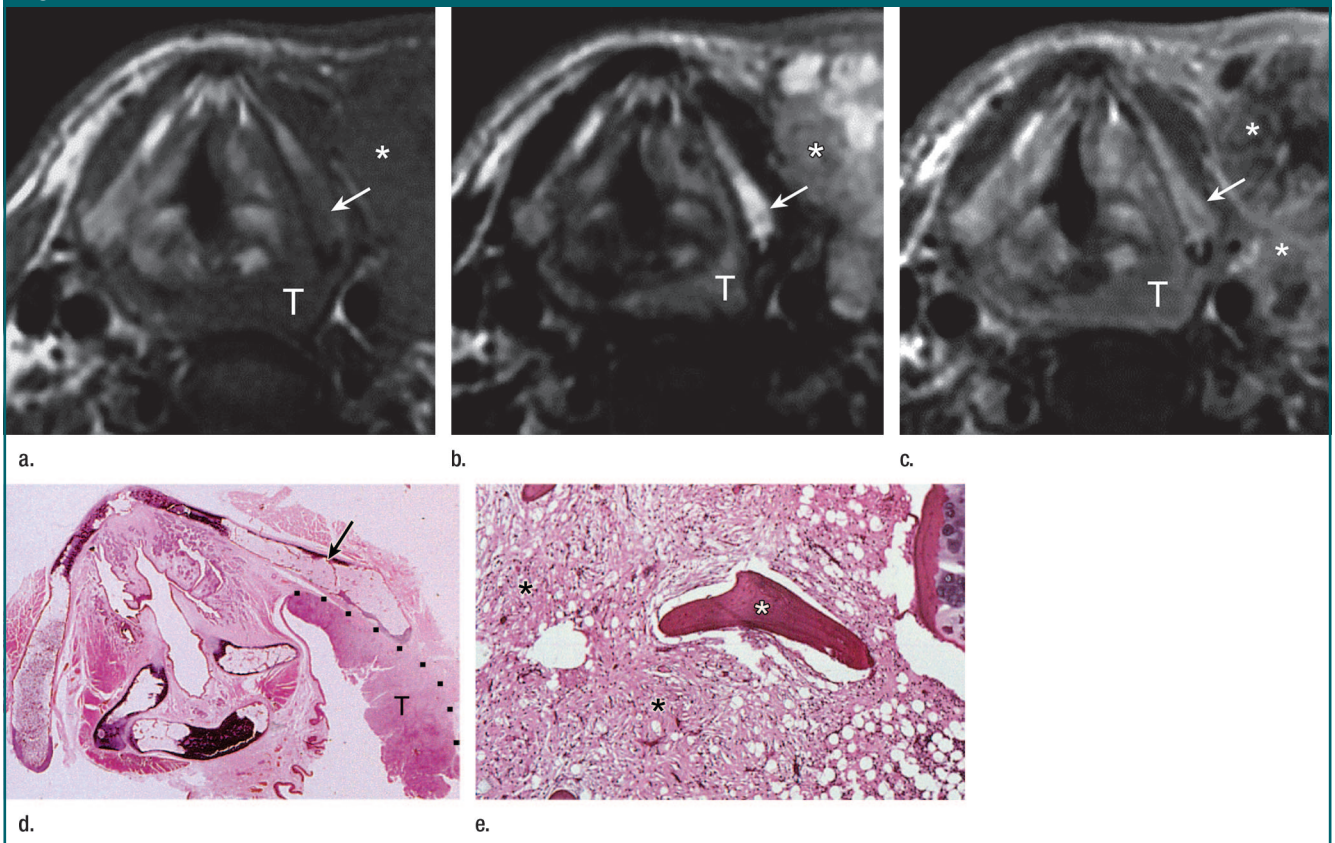

Figure 2: Inflammation of thyroid cartilage. Axial MR imaging findings were false-positive for neoplastic invasion with the old and true-negative for neoplastic invasion with the new diagnostic criteria. **(a)** T1-weighted spin-echo MR image (420/12) obtained at glottic level shows left-sided piriform sinus tumor *(T)* with intermediate to low signal intensity. Adjacent left thyroid lamina (arrow) shows similar intermediate to low signal intensity. **(b)** T2-weighted fast spin-echo MR image (4400/80) obtained at same level as **a** shows that the tumor *(T)* has moderately high signal intensity, while the adjacent thyroid lamina (arrow) has much higher signal intensity than the soft-tissue component of the tumor itself. **(c)** T1-weighted spin-echo MR image (420/12) obtained after intravenous administration of contrast material shows enhancement of the tumor mass *(T)* and stronger enhancement of the thyroid lamina (arrow) relative to the adjacent tumor mass. According to the old diagnostic MR imaging criteria, neoplastic invasion of the thyroid cartilage should be suspected (Table 1). According to the new criteria, the most likely diagnosis is inflammation of the thyroid cartilage without neoplastic invasion because the signal intensity on **b** is higher than that of the adjacent tumor and the enhancement of the thyroid cartilage is stronger than the tumor enhancement. Note large necrotic lymph node metastasis on the left (∗ in **a–c**). **(d)** Corresponding axial slice from surgical specimen at same level shows that the left thyroid lamina is not invaded by tumor (arrow). The tumor *(T)* arises from the lateral wall of the left piriform sinus. Black dots = lateral tumor borders. (Hematoxylin-eosin stain.) **(e)** Detail in left posterior thyroid lamina (enlargement of area in **d**) shows severe inflammatory changes within the medullary space, with fibroblasts, lymphocytes, macrophages, and remodeled bone trabeculae (∗). (Hematoxylin-eosin stain; original magnification, ×6.25.)

Figure 3

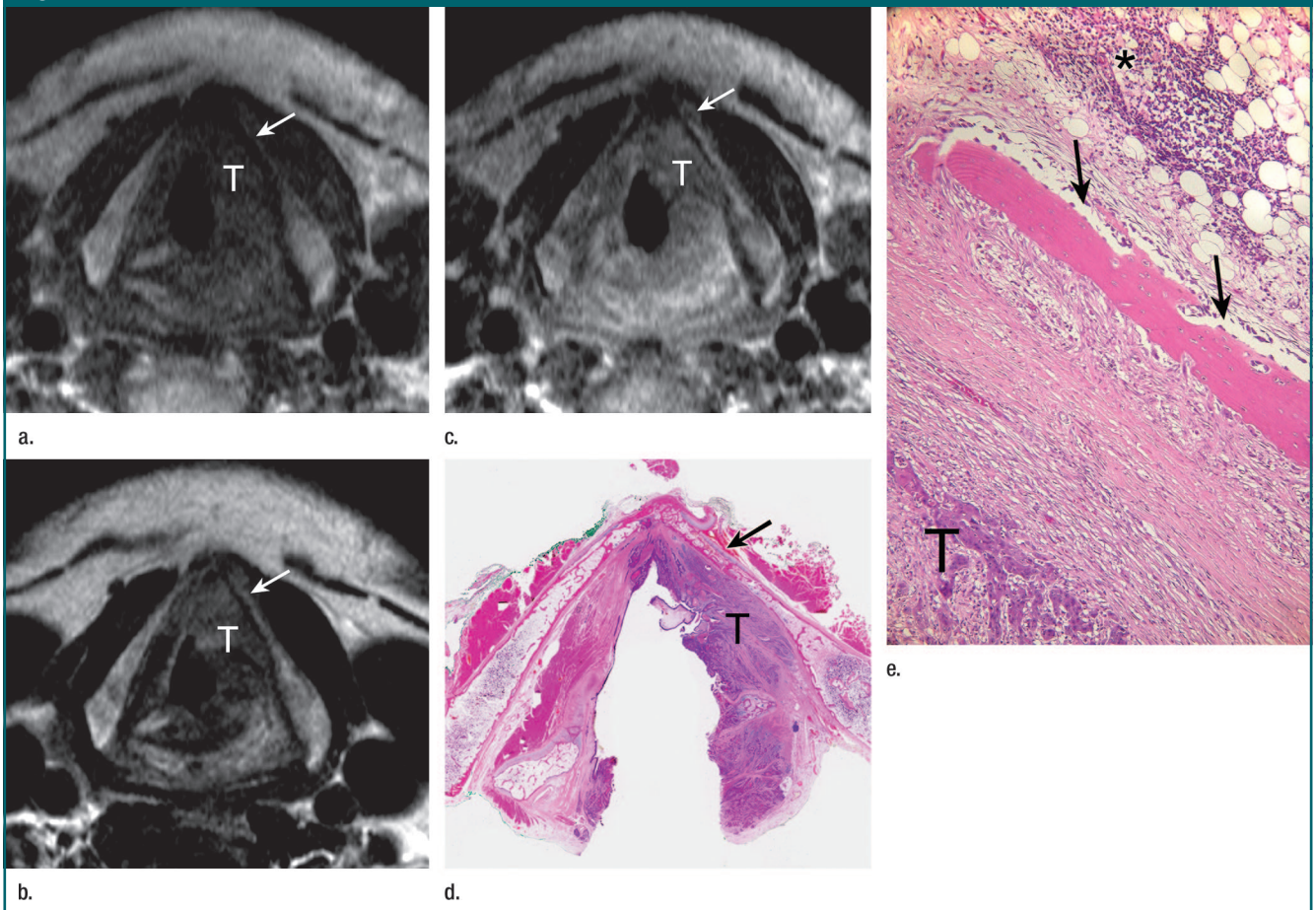

Figure 3: Inflammation of thyroid cartilage with more subtle findings at MR imaging than in Figure 2. (Axial MR imaging findings were false-positive for neoplastic invasion with the old and true-negative for neoplastic invasion with the new diagnostic criteria). **(a)** T1-weighted MR image (330/12) obtained at supraglottic level shows left-sided laryngeal tumor *(T)* with intermediate to low signal intensity. Adjacent left thyroid lamina (arrow) also shows intermediate to low signal intensity. **(b)** T2-weighted fast spin-echo MR image (4451/100) shows that the tumor *(T)* has intermediate signal intensity, while the adjacent thyroid lamina (arrow) has slightly higher signal intensity. **(c)** T1-weighted MR image (330/12) obtained after intravenous administration of contrast material shows moderate enhancement of the tumor mass *(T)* and slightly stronger enhancement of the adjacent thyroid lamina (arrow). According to the old diagnostic MR imaging criteria, neoplastic invasion of the thyroid cartilage should be suspected. According to the new diagnostic MR imaging criteria (Table 1), although the findings are more subtle, the most likely diagnosis is inflammation of the thyroid cartilage without neoplastic invasion. **(d)** Corresponding axial slice from surgical specimen at same level shows that the left thyroid lamina (arrow) is not invaded by tumor *(T)*. Deep purple serpiginous areas seen within the thyroid cartilage in the vicinity of the arrow correspond to remodeled bone trabeculae. The tumor arises from the left ventricular fold. (Hematoxylin-eosin stain.) **(e)** Detail in left thyroid lamina (enlargement of area in **d**) shows severe inflammatory changes within the medullary space (*), with inflammatory cells and fibroblasts, as well as marked bone remodeling (arrows). *T* = tumor. (Hematoxylin-eosin stain; original magnification, ×20.)

with or without inflammatory changes at histopathologic examination.

Statistical Comparisons between Combinations of Pulse Sequences

Statistical comparison of the results of different combinations of MR imaging sequences for scores 3–5 (Table 2) showed that there was no significant difference between the old and the new criteria in terms of sensitivity ($P \geq .32$). However, T1/T2 new and T1/T1 + Gd new showed a significantly higher specificity for all cartilages considered together ($P < .001$ and $P < .002$, respectively). The increase in specificity was highest in the thyroid cartilage ($P < .001$) and was less evident in the cricoid ($P = .01$) and arytenoid ($P = .05$) cartilage. When we compared T1/T2 new with T1/T1 + Gd new, there was no significant difference in sensitivity or specificity ($P \geq .27$).

The ROC curves for all cartilages considered together and the corresponding A_z values for the old and new MR imaging criteria are shown in Figure 4. The A_z was 0.92 for T1/T2 old, 0.93 for T1/T1 + Gd old, 0.94 for T1/T2 new, and 0.94 for T1/T1 + Gd new, suggesting that the new MR imaging criteria performed better as a diagnostic modality. Although the observed difference in A_z values was quite small, pairwise comparisons of A_z values

showed the following: *(a)* the A_z for T1/T2 new was significantly larger than that for T1/T2 old ($P = .01$), *(b)* the A_z for T1/T1 + Gd new was significantly larger than that for T1/T1 + Gd old ($P = .01$), and *(c)* there was no significant difference between the A_z for T1/T2 new and that for T1/T1 + Gd new ($P = .99$). The ROC curves did not cross, which satisfies an important criterion for the use of the A_z measure in this comparison (22,23).

Discussion

The MR imaging findings of neoplastic invasion of the laryngeal cartilage that are currently used have been established with variable technical parameters (0.6 T vs 1.5 T), variable methods (in vitro vs in vivo studies), and relatively small numbers of cases (12–15). In all studies published so far, to our knowledge, the diagnosis of neoplastic cartilage invasion at MR imaging was mainly based on the criteria that are currently widely accepted and that we have termed "established" or "old," as summarized in Table 1 (2,3,5,6, 12–15).

Results of our current study, which was performed in a large series, confirm that the established MR imaging criteria may lead to false-positive results in a considerable number of instances, because reactive inflammation, edema, and fibrosis in the vicinity of the tumor may display similar diagnostic features as cartilage infiltrated by tumor. The specificity of MR imaging with the established criteria was particularly poor for the thyroid cartilage, in which peritumoral inflammatory changes were most common, and was moderately high in the cricoid and arytenoid cartilages, in which peritumoral inflammatory changes were less common (Table 2). Although results of the present study showed that sensitivity with the new criteria was very good for the thyroid and cricoid cartilages, it was somewhat lower for the arytenoid cartilage. This was due to the presence of a higher number of cases with microscopic invasion.

Figure 4

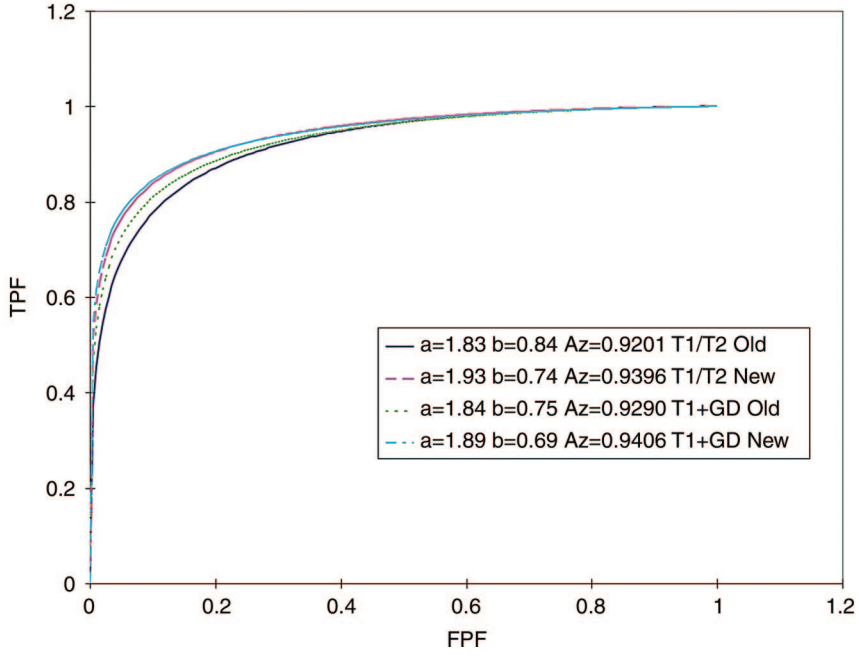

Figure 4: Graph shows conventional binormal ROC curves and corresponding A_z values for prediction of invasion of any of the laryngeal cartilages considered together. For statistical comparison of A_z values, see the Results section of the text. *FPF* = false-positive fraction, *TPF* = true-positive fraction.

The use of our modified (new) diagnostic MR imaging criteria enabled us to significantly increase the specificity ($P < .001$) in assessing neoplastic cartilage invasion without affecting sensitivity (Table 2). This was possible because the use of the new criteria often enabled us to distinguish between tumor and peritumoral inflammation, thus leading to a significant reduction of the number of false-positive assessments. The significant increase in specificity ($P < .001$) was most striking in the thyroid cartilage, where inflammatory changes are most common.

Analysis of our ROC curves indicates that the new MR imaging criteria are more accurate than the old criteria, although the observed increase in A_z was quite small. Because statistical comparison between T1/T2 new and T1/T1 + Gd new showed no significant difference between these two pulse sequence combinations, assessment of neoplastic cartilage invasion may thus be performed with T1-weighted or T2-weighted sequences, and the administration of gadolinium chelates may not be necessary for this purpose.

Results of the current study indicate that only laryngeal cartilages with a similar signal intensity relative to tumor on T2-weighted images or similar enhancement on gadolinium-enhanced images as the adjacent tumor should be regarded as invaded by tumor, whereas cartilages with a higher signal intensity on T2-weighted images and a stronger enhancement after injection of gadolinium chelates should not be considered to be invaded. MR imaging may therefore be used for a more precise selection of the appropriate surgical procedure, which is influenced not only by the local extent of tumor but also by the presence or absence of cartilage invasion.

Some limitations of our study were related to its retrospective design, such as the absence of fat-saturated sequences. However, most results published in the literature on cartilage invasion in squamous cell carcinoma of the larynx and hypopharynx (2,3,5,8–13) are based on the use of a combination of T1-weighted, T2-weighted, and gadolinium-enhanced T1-weighted images, and fat-satura-

tion techniques have so far not been used routinely in this area. In the only study to our knowledge in which fat-saturated MR images were compared with histologic findings, Atula et al (24) reported an accuracy of 50% and a high rate of false-positive and false-negative findings. Although fat saturation was not included in the MR imaging protocols of our retrospective study, it is possible that the addition of such sequences might further enhance the signal intensity difference between inflammatory and neoplastic cartilage changes. It could therefore be worthwhile to include additional fat-saturated sequences in the protocol of a future prospective study.

In our study, visual analysis of the signal intensity of laryngeal cartilages was performed by using the adjacent tumor mass as an internal reference standard, and no specific regions of interest were measured. Although this may be a straightforward way of comparing differences in signal intensity of the tumor and the adjacent cartilages in clinical practice, future prospective studies could include additional region of interest measurements to confirm our findings. Results of our study may have an impact on T staging, because neoplastic cartilage invasion changes the T stage (1). The presence of neoplastic cartilage invasion may also influence the choice of treatment (partial vs total laryngectomy or radiation therapy). Recently, Ljumanovic et al (25) have shown that the signal intensity behavior of the laryngeal cartilage at MR imaging was correlated with the prognosis after radiation therapy of glottic squamous cell carcinoma. An intermediate signal intensity of cartilage on T2-weighted images was correlated with a less favorable response, whereas a high signal intensity on T2-weighted images did not affect local control ($P < .001$). Therefore, the authors suggested that intermediate signal intensity might correspond to neoplastic cartilage invasion, whereas high signal intensity might correspond to inflammatory tissue. Results of our current study may support this hypothesis.

In summary, results of our study support the hypothesis that visualization of higher signal intensity on T2-weighted MR images and stronger enhancement in the cartilage compared with the adjacent tumor suggests peritumoral inflammation within the laryngeal cartilage, whereas a similar signal intensity on both T2-weighted and contrast-enhanced T1-weighted images corresponds to intracartilaginous tumor. Thus, the diagnostic MR imaging criteria we propose have the potential to improve the distinction between tumor tissue and peritumoral inflammation.

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