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LARYNGOLOGY

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Staging of laryngeal cancer: endoscopy, computed tomography and magnetic resonance versus histopathology

Abstract An accurate pretherapeutic staging of laryngeal cancer is required for optimal treatment planning and for evaluation and comparison of the results of different treatment modalities. In this study, 45 consecutive patients with neoplasms of the larynx, treated surgically, were included in a prospective pretherapeutic staging protocol that included indirect laryngoscopy, direct microlaryngoscopy, contrast-enhanced computed tomography (CT) and Gd-DTPA-enhanced magnetic resonance imaging (MRI). The surgical specimens were cut in whole-organ slices parallel to the plane of the axial CT and MR images. The histologic findings were then compared with clinical findings, CT and MRI. These findings showed that clinical evaluation failed to identify tumor invasion of the laryngeal cartilages and extralaryngeal soft tissues, resulting in a low staging accuracy (55%). Many pT4 tumors were clinically understaged. The combination of clinical/endoscopic evaluation and either CT or MRI resulted in a significantly improved staging accuracy (80% vs 87%, respectively). MRI was significantly more sensitive but less specific than CT in detecting neoplastic cartilage invasion. MRI tended to overestimate neoplastic cartilage invasion to possibly result in overtreatment, while CT was found to underestimate neoplastic cartilage invasion and could lead to inadequate therapeutic decisions.

Key words Laryngeal neoplasms · Tumor staging · Endoscopy · Magnetic resonance imaging · Computed tomography

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Introduction

One of the most important factors in treatment planning of laryngeal cancer is the accuracy of pretherapeutic staging. However, the limitations of clinical and endoscopic evaluation to assess the exact extension of laryngeal carcinomas are well recognized [31, 38]. The anterior commissure and subglottic region can be hidden by bulky tumors. Deep tumor extension such as infiltration of pre-epiglottic and paraglottic spaces, cartilaginous skeleton and extralaryngeal structures also cannot be evaluated by endoscopy.

Laryngeal tomography, contrast laryngography and xeroradiography have all been used to evaluate tumor extent. Each of these methods has been found unreliable in assessing deep tumor spread and cartilage invasion [33]. Since 1976, computed tomography (CT) has become a reliable technique for evaluating most tumors of the head and neck [41] and is now considered an important radiologic adjunct in the pretherapeutic work-up of laryngopharyngeal cancer [3, 14, 19, 27]. Nevertheless, CT of the larynx has its limitations, especially in determining cartilage invasion [2, 4, 6, 8, 10, 17], due to the irregular mix of calcified, ossified and non-calcified cartilage. However, neoplastic invasion of the laryngeal cartilage can have major therapeutic implications. Cartilage involvement reduces the chances of radiotherapy of being successful and may also preclude voice preserving surgery, total laryngectomy becoming mandatory [11, 22].

Recently, magnetic resonance imaging (MRI) has proved to be a reliable diagnostic method for the evaluation of laryngeal cancer. Based on the literature, MRI appears to be more suitable than CT in predicting neoplastic cartilage invasion [6, 9, 12, 13, 39]. However, it has still not been determined which imaging modality, CT or MRI, should be used in the pretherapeutic staging of laryngeal cancer.

To our knowledge, no data are available comparing the impact of clinical/endoscopic examination, CT and MRI, on pretherapeutic staging of laryngeal cancers, while only a few reports are available comparing the results of CT and MRI against histology [6, 10]. The purpose of the pre-

sent study was to assess the accuracy of preoperative CT, MRI and clinical/endoscopic staging of laryngeal tumors by comparing clinical and imaging findings of each modality with histologic cross-sections of surgical specimens and to analyze the impact of each on pretherapeutic staging.

Materials and methods

Patients

Between October 1992 and March 1996, 45 surgically treated patients with neoplasms of the larynx were included in a prospective pretherapeutic staging protocol including indirect laryngoscopy, direct microlaryngoscopy, CT and MRI. There were 44 males and 1 female, with a mean age of 60 years (range, 44–87 years). Forty-three patients had squamous cell carcinomas, 1 patient had an undifferentiated nasopharyngeal carcinoma and 1 patient had an adenocarcinoma. There were 7 supraglottic, 1 subglottic, 5 glottic-supraglottic, 15 glottic-subglottic and 17 transglottic tumors. Forty-one patients underwent total laryngectomy and 4 voice-preserving laryngectomies (3 supraglottic laryngectomies and 1 subtotal laryngectomy).

Clinical and endoscopic evaluation

All patients underwent indirect laryngoscopy. If mobility of the larynx could not be evaluated reliably, transnasal fiberoptic laryngoscopy was also performed. Thereafter, panendoscopy with microlaryngoscopy and photographic documentation was performed under anesthesia in all patients.

CT and MRI techniques

CT was performed with a Somatom Plus Scanner (Siemens, Erlangen, Germany). Axial slices of 2 mm thickness and 2 mm interspace gaps were taken from the base of the tongue to the trachea after intravenous administration of 150 ml ioxithalamate-meglumine (Telebrix; Guerbet, Aulnay-s. Bois, France).

MRI was performed on a Signa 1.5 T Perf. Plus unit (GE Medical Systems, Milwaukee, Wis., USA) with an anterior neck coil. The MRI protocol consisted of axial T2-weighted fast spin echo (FSE) and T1-weighted spin echo (SE) images. After intravenous administration of gadolinium-DTPA (Magnevist, Schering, Germany), axial, sagittal and coronal T1-weighted SE images were obtained. The slice thickness was 3 mm or 4 mm (in large tumors) with 0.3, 0.4 or 1-mm intersection gaps.

CT and MRI were obtained within a maximum interval of 2 weeks in each patient and reviewed separately by three independent radiologists in a blinded prospective fashion. Surgical resections were performed 1–2 weeks after the last imaging study.

Histologic preparations

All surgical specimens underwent fixation in 4% formaldehyde for 72 h and decalcification in De-cal-Histol. Decalcif. Agent (Pational Diagnostic, Mainville, N.J., USA) for 2 weeks. Axial whole-organ slices were cut at a thickness of 3–5 mm parallel to the plane of the axial CT and MR images as described by Michaels and Gregor [29]. In selected cases additional axial slices were cut at a thickness of 1 mm. At each level at least one slice was processed for microscopic examination and stained with hematoxylin-eosin.

Classification of primary tumors

Lesions were staged for tumor (T) according to the International Union against Cancer, 1992 TNM classification and 1993 TNM Supplement [16, 37]. Tumors with extension to the paraglottic space were radiologically and pathologically staged as T3 [20, 28, 38]. Neoplastic infiltration of the arytenoid did not influence the T-classification.

Statistical analysis

Statistical comparison of the results was done by using the two-tailed exact test for matched pairs for a small sample size based on binomial distribution [1].

Results

Histopathologic analysis and pT staging

The anterior commissure was invaded in 31 specimens, the subglottic region in 33 of 42 specimens. Tumor involvement of the anterior commissure in 2 cases and subglottis in 3 cases was entirely submucosal. Tumor involvement of the pre-epiglottic space was observed in 12 of 45 specimens and was found in the paraglottic space in 34 of 42 specimens. Neoplastic invasion of cartilages including the perichondrium was present in 32 of 45 specimens: thyroid cartilage ($n = 19$), cricoid cartilage ($n = 18$), and arytenoid cartilage ($n = 25$). Five tumors were classified as pT2, 21 as pT3 and 19 as pT4.

Clinical/endoscopic findings and staging

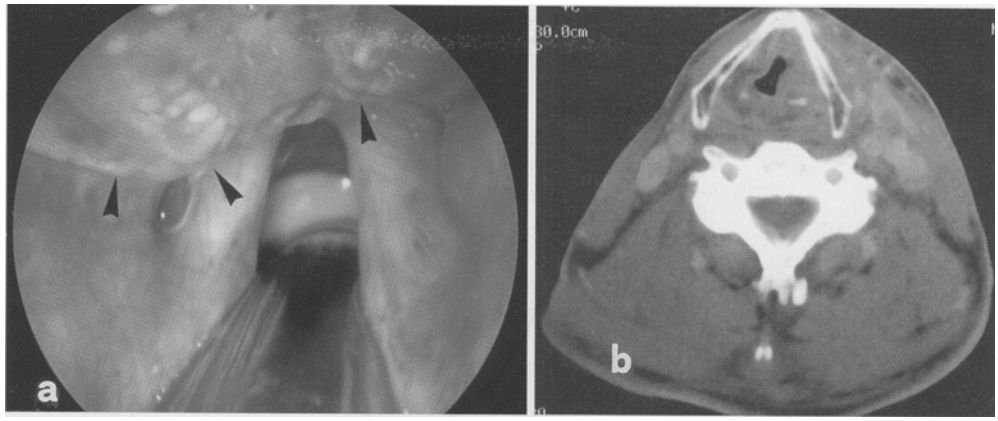
Based on indirect or fiberoptic laryngoscopy, vocal cord mobility was diminished or absent in 33 patients. In 30 cases vocal cord fixation corresponded at histopathology to tumor invasion of the paraglottic space and in 3 cases each to invasion of the ventricular fold, of the arytenoid cartilage or periarytenoid region.

Table 1 CT findings of tumor involvement in laryngeal cartilages in 41 total laryngectomy specimens and 3 supraglottic and 1 subtotal laryngectomy specimens

Laryngeal cartilage	*n*	True positive	True negative	False positive	False negative	Accuracy %
Thyroid	45	9	25	1	10	75
Cricoid	41	15	19	4	3	83
Arytenoid	82	16	50	7	9	80
Overall	168	40	94	12	22	80

Table 2 MR findings of tumor involvement in laryngeal cartilages in 41 total laryngectomy specimens and 3 supraglottic and 1 subtotal laryngectomy specimens

Laryngeal cartilage	*n*	True positive	True negative	False positive	False negative	Accuracy %
Thyroid	45	19	13	13	0	71
Cricoid	41	18	16	7	0	83
Arytenoid	82	22	52	5	3	90
Overall	168	59	81	25	3	83



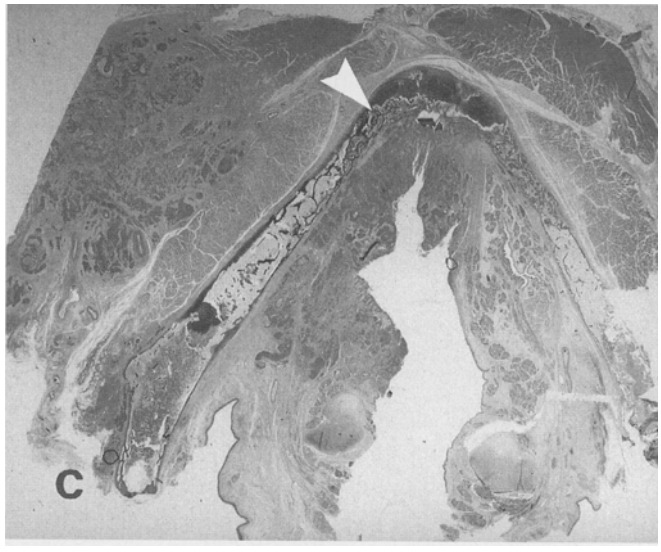


Fig. 1 a–c Supraglottic squamous cell carcinoma with invasion of the thyroid cartilage. **a** Endoscopic view: tumor mass at the laryngeal surface of the epiglottis (*arrowhead*). **b** Contrast-enhanced axial CT scan at the supraglottic level shows no signs of thyroid cartilage invasion. **c** Histologic axial slice from specimen obtained at the same level as **b** shows neoplastic invasion of the thyroid cartilage at the anterior commissure (*arrowhead*)

On microlaryngoscopy, the anterior commissure was invaded in 28 of 45 cases, and the subglottic region in 27 cases. Anterior commissure and subglottic involvement was missed at endoscopy in 3 and 6 cases, respectively. In 4 of these 9 cases, the anterior commissure and subglottic region were hidden behind a bulky tumor mass which in one case was essentially submucosal, so that only deep biopsies obtained during microlaryngoscopy allowed definitive diagnosis. In the 5 other cases, tumor extension was essentially submucosal.

According to the clinical and microlaryngoscopic examination, 12 laryngeal tumors were classified as T2, 31 as T3 and 2 as T4. Twenty-one of 45 cases were staged incorrectly: 13 pT4 tumors were clinically classified as T3, 4 pT4 tumors as T2 and 3 pT3 tumors as T2. All cases were understaged. The accuracy of clinical staging was 25 of 45 (55%). Clinical evaluation failed to classify correctly 1 tumor with invasion of the paraglottic space, 2 tumors with invasion of the pre-epiglottic space and 17 tumors with neoplastic invasion of tissues out of the larynx [tumor growths through cartilage (n = 12), through the cricothyroid membrane (n = 5)].

CT and MRI findings and staging

According to the CT findings (Table 1), 6 laryngeal tumors were classified as T2, 23 as T3, and 16 as T4. Nine of 45 cases were staged incorrectly: 5 pT4 tumors were classified by means of CT as T3, 1 pT4 as T2 and 3 pT3 as T4; thus, 6 cases were understaged and 3 overstaged. According to combined clinical/endoscopic and CT evaluation, 6 laryngeal tumors were classified as T2, 23 as T3, and 16 as T4, taking the higher stage of the two staging modalities into account. With MRI findings (Table 2), 4 laryngeal tumors were classified as T2, 18 as T3, and 23 as T4. Six of 45 cases were staged incorrectly: 4 pT3 tumors were classified by means of MRI as T4, 1 pT2 as T4 and 1 pT4 as T3. Thus, 5 cases were overstaged and 1 case understaged. According to combined clinical/endoscopic and MRI evaluations, 4 laryngeal tumors were classified as T2, 18 as T3, and 23 as T4, taking the higher stage of the two staging modalities into account.

For assessment of the anterior commissure, subglottic region, and pre-epiglottic and paraglottic spaces, there were no significant differences between CT and MRI. With regard to assessment of cartilage neoplastic invasion, MRI had a significantly higher sensitivity (but with numerous false-positive findings) than CT (P = 0.001), whereas CT had a significantly higher specificity (with numerous false-negative findings) (Fig. 1) than MRI (P = 0.009). However, there was no statistical difference between the accuracy of CT and MRI in detecting cartilage invasion.

The accuracy of clinical staging was 55%. The accuracy of combined clinical and CT staging was 80%, and that of combined clinical and MRI staging was 87%. Both imaging modalities combined with clinical/endoscopic evaluation had a significantly higher accuracy than clinical staging alone (clinical vs clinical and CT staging: P = 0.001; clinical vs clinical and MRI staging: P = 0.001). There were no statistical differences between combined clinical and CT staging and combined clinical and MRI staging.

Discussion

Clinical staging alone of laryngeal tumors has failed to correctly estimate the true extension of tumor in a high percentage of cases. In the present study we observed in-

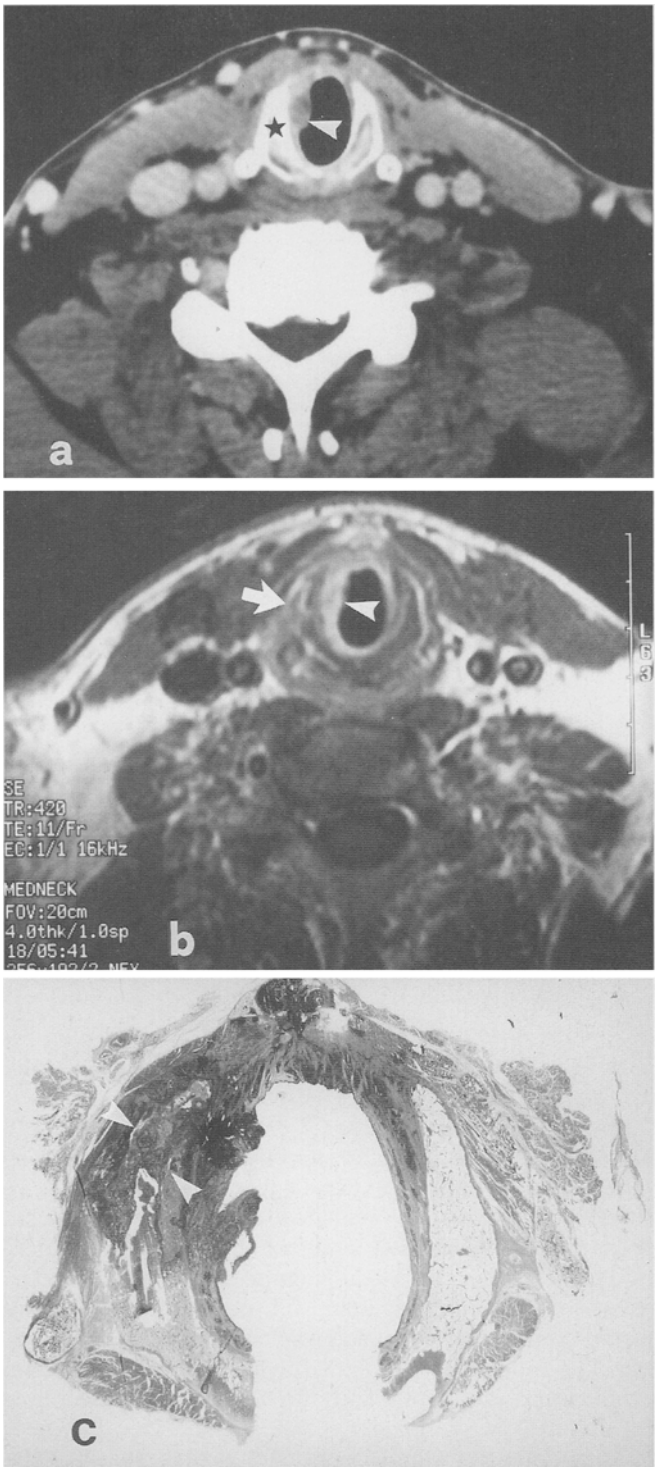


Fig. 2 a–c Glottic-subglottic squamous cell carcinoma with a fixed vocal cord. **a** Contrast-enhanced axial CT scan obtained at the subglottic level showing a right-sided tumor mass (*arrowhead*) and asymmetric sclerosis of the cricoid cartilage suggesting neoplastic invasion (*asterisk*). **b** T1-weighted spin-echo MR image after administration of contrast material shows enhancement of the subglottic mass (*arrowhead*) and of the right cricoid cartilage (*arrow*), suggesting neoplastic cartilage invasion. **c** Histologic axial slice obtained at the same level as **a** and **b** shows a tumor invading the right cricoid cartilage (*arrowhead*)

accurate clinical staging in 20 of 45 laryngeal tumors (45%). These findings are quite similar to those reported by Pillsbury and Kirchner [31] and Sulfaro et al. [38].

The anterior commissure and the subglottic region are often hidden by bulky tumors. The oncologic importance of the anterior commissure has been emphasized by many authors [5, 24]. It is the preferential pathway for cancer extension to the anterior angle of the thyroid cartilage and downward to the region of the subcommissure and cricothyroid membrane. In our study, anterior commissure invasion was missed by endoscopy in 3 cases. In these 3 cases, anterior commissure involvement was diagnosed by CT and MRI.

Tumor extension to the subglottic region is a contraindication for voice-preserving surgery. Therefore, a correct pretherapeutic evaluation of the subglottis is mandatory for optimal treatment planning. In the present study, subglottic tumor extension was missed during endoscopy in 6 cases. CT evaluation was correct in 2 of these cases and MRI in 3 cases.

All clinical/endoscopic staging errors consisted of an underestimation that resulted from a failure to clinically identify invasion of the paraglottis, pre-epiglottic space and destruction of laryngeal cartilage with extralaryngeal tumor invasion. As a consequence, many pT4 laryngeal tumors were unrecognized clinically. Detection of cartilage invasion is important, since its presence precludes conservation laryngeal surgery in many cases and is associated with an increased risk of perichondritis, necrosis and tissue edema following radiation therapy. Therefore many authors assume that radiotherapy is not an appropriate treatment for laryngeal carcinomas with neoplastic cartilage invasion [21, 35, 42].

CT and MRI evaluation and staging

CT assessments of the paraglottic space were correct in 88% and MRI in 90%. However, there was no statistically significant difference between CT and MRI. Tumors arising in the ventricle invade first the paraglottic space and then both the supraglottic and subglottic areas without being recognizable by endoscopic examination [23].

CT assessment of the pre-epiglottic space was correct in our study in 95% of cases and MRI in 93%. Again, there was no statistical difference between CT and MRI. Our results of CT assessment of the paraglottic and pre-epiglottic space were slightly better than those reported in the literature [7, 13, 15]. This was also probably due to our imaging technique using thin slices.

According to the literature, CT accurately demonstrates gross cartilage invasion, especially in the presence of extralaryngeal tumor spread, but fails to detect minor cartilage invasion in many cases [4, 6, 10, 17, 26]. The ability of CT to detect neoplastic invasion varies widely, with reported sensitivities of 46–66% and specificities of 84–94% [6, 10]. In the present study we found a sensitivity of 64% and a specificity of 88%. The irregular calcification pattern of the thyroid cartilage does not correlate

with tumor invasion nor can normal and pathologic cartilage be distinguished on the basis of density values [4, 8, 17, 26]. In the cricoid and arytenoid cartilage, however, asymmetric irregular sclerosis can suggest cartilage invasion (Fig. 2) [8, 30]. MRI shows details of non-ossified and ossified cartilage better than CT. The reported overall sensitivity of MRI in the detection of neoplastic cartilage invasion is 89% and the specificity varies between 82% and 88% [6, 10]. In our study of 45 cases, we found a sensitivity of 95% and a specificity of 76%. MRI had a higher sensitivity for detecting neoplastic cartilage invasion than CT, but also had a significantly lower specificity. As recently reported, this is caused by severe inflammatory changes, fibrosis and extramedullary hematopoiesis within the cartilage which result in a higher rate of false-positive MRI [6]. Although there were no statistical differences found between CT and MRI in overall accuracy in detecting neoplastic cartilage invasion, the high false-positive rate of MRI may result in overtreatment to the extreme, a needless total laryngectomy. In contrast, CT tends to have a high false-negative rate for neoplastic cartilage invasion and therefore may lead to inappropriate partial laryngectomy or inadequate radiotherapy. Knowledge of the potential pitfalls of both imaging techniques, namely underestimation of cartilage invasion with CT and overestimation with MRI, is essential in deciding upon the appropriate therapy. As a result, a careful interdisciplinary interpretation of CT and MRI findings with a head and neck surgeon and a radiation oncologist, taking into account clinical and endoscopic findings, is mandatory for avoiding inappropriate treatment.

The usefulness of CT and MRI in the pretreatment staging of laryngeal carcinoma has been emphasized in many studies [18, 32, 34]. Several studies have compared CT data [2–4, 25, 26, 36, 38], while a few studies have compared MRI data with the histology of whole-organ sections [6, 9, 10, 40]. However, to our knowledge, no data are available comparing the results of endoscopic findings with CT and MRI and anatomically matched histologic whole organ sections analyzing the impact of each diagnostic method on pretherapeutic staging.

Our present study has shown that the accuracy of combined clinical and CT staging was 80% and that of combined clinical and MRI staging was 87%. That this difference is not statistically significant is due to the equivalent overall accuracy of each study in detecting cartilage invasion by tumor despite different sensitivities and specificities.

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