Head and neck radiology

Original article

Atypical squamous cell carcinoma of the larynx and hypopharynx: radiologic features and pathologic correlation

M. Becker[1], G. Moulin[2], A.-M. Kurt[3], P. Zbären[4], P. Dulgerov[5], F. Marchal[5], P. Zanaret[6], W. Lehmann[5], D. A. Rüfenacht[1], F. Terrier[1]

[1] Department of Radiology, Geneva University Hospital, Rue Micheli-du-Crest 24, CH-1211 Geneva, Switzerland
[2] Department of Radiology, University Hospital La Timone, Marseille, France
[3] Department of Pathology, Geneva University Hospital, Rue Micheli-du-Crest 24, CH-1211 Geneva, Switzerland
[4] Department of Head and Neck Surgery, University Hospital Bern, Bern, Switzerland
[5] Department of Head and Neck Surgery, Geneva University Hospital, Rue Micheli-du-Crest 24, CH-1211 Geneva, Switzerland
[6] Department of Head and Neck Surgery, University Hospital La Timone, Marseille, France

Abstract. The objective of this study was to analyze the radiologic features of atypical forms of squamous cell cancer and correlate them with clinical, endoscopic, and histopathologic findings. The CT and MRI images of 31 patients with atypical forms of squamous cell carcinoma were reviewed retrospectively and the radiologic findings were correlated with clinical, endoscopic, and histopathologic findings. Histopathologic diagnoses included undifferentiated carcinoma of nasopharyngeal type ($n = 8$), verrucous carcinoma ($n = 18$), spindle cell carcinoma ($n = 3$), and basaloid cell carcinoma ($n = 2$). Undifferentiated carcinoma of nasopharyngeal type was located in the supraglottis or piriform sinus beneath an intact mucosa and initial endoscopic biopsy was most often negative. The discrepancy between an intact mucosa at endoscopy and a solid mass with homogenous enhancement at CT or MRI was characteristic for these tumors and warranted further investigations to obtain the definitive histologic diagnosis. Verrucous carcinoma displayed characteristic clinical, radiologic, and pathologic features, namely, an exophytic tumor arising from the glottic level displaying a rugged surface with finger-like projections but with only minor submucosal infiltration. Spindle cell carcinoma appeared as a polypoid mass with a thin stalk arising from the supraglottis. Basaloid cell carcinoma displayed a distinct lobulated enhancement pattern which was observed on contrast-enhanced T1-weighted SE images. Although the MR and CT features of atypical forms of squamous cell carcinoma cannot be considered pathognomonic they should raise the differential diagnosis even if endoscopic biopsy has been negative. The radiologist's awareness of the appearance of these unusual tumors on CT and MR images may greatly facilitate the diagnostic work-up and helps to guide the endoscopist to the adequate biopsy site in order to establish the correct diagnosis.

Key words: Larynx – CT – MR – Neoplasms

Introduction

The vast majority of laryngeal and hypopharyngeal neoplasms are squamous cell carcinomas with different degrees of differentiation [1–5]. The term "atypical forms of squamous cell carcinoma" is used for certain distinct histopathologic variants with a different biologic behavior, namely, undifferentiated carcinoma of nasopharyngeal type, verrucous carcinoma, spindle cell carcinoma, basaloid cell carcinoma, adenoid squamous cell carcinoma, and giant cell carcinoma [1–5]. According to the literature, 2–7 % of all laryngeal and hypopharyngeal tumors are atypical forms of squamous cell carcinoma [1, 2]. These tumors may differ from the common type of squamous cell carcinoma in several aspects regarding diagnosis, prognosis, and therapeutic approach [1–5]. Squamous cell carcinoma usually presents with obvious mucosal abnormalities and is therefore readily diagnosed with endoscopy, whereas some atypical forms of squamous cell carcinoma do not primarily involve the mucosal surface. It is well recognized that the diagnosis of submucosal tumors of the larynx and hypopharynx is often delayed because endoscopic biopsies may be initially negative [6–8]. Although a reliable histologic characterization of epithelial and some mesodermal tumors is often impossible with CT and MRI, it appears that certain morphologic features should alert the radiologist to the presence of an atypical laryngeal or hypopharyngeal neoplasm. If the mucosa appears normal at endoscopy, the role of cross-sectional imaging is not only

Correspondence to: M. Becker

to delineate the extent of submucosal infiltration, but also to guide the endoscopist to the most appropriate biopsy site. Deep transmucosal biopsies are usually required to allow the correct diagnosis [6–8].

In a recent report we analyzed and correlated with histopathology the radiologic features of a variety of non-squamous cell tumors including sarcomatous as well as lymphoreticular and lipomatous tumors, tumors of the minor salivary glands, and the so-called vasoformative tumors [9]. Although atypical forms of squamous cell carcinoma have received considerable attention in the clinical and pathologic literature, our review of the literature revealed no report on the MRI and CT features of the so-called atypical forms of squamous cell carcinoma. The objective of our current study was to describe and analyze the radiologic features of a variety of atypical squamous cell cancers, to correlate the radiologic findings with histopathologic results, to familiarize radiologists with these unusual histologic types of neoplasms, and to discuss the clinical role of CT and MRI in the pretherapeutic work-up of these lesions.

Materials and methods

Between 1992 and 1997, 1721 patients with neoplasms of the larynx and hypopharynx were seen at three institutions. According to the final histologic diagnosis, 1634 patients (95 %) had squamous cell carcinoma of the common type and 35 (2 %) had non-squamous cell tumors. Atypical forms of squamous cell carcinoma were diagnosed in 52 patients (3 %), namely in 49 men and 3 women with a mean age of 62 years (age range 43–79 years). Among these 52 patients we retrospectively identified 31 patients who had complete clinical, radiologic, endoscopic, surgical, and pathologic records, and excluded 21 patients in whom imaging studies had not been done or documentation was incomplete. The 31 patients with complete documentation formed the basis of our study.

Prior to treatment, 22 patients underwent contrast-enhanced dynamic, incremental CT, 3 patients underwent MRI, and 6 patients underwent both examinations. At all three institutions, CT and MRI images were obtained using standard imaging protocols for the larynx and hypopharynx. The CT studies were obtained after intravenous bolus injection of iodinated contrast material (total dose: 40–45 g iodine). Contiguous axial 1.5- to 3-mm thin sections parallel to the plane of the vocal cords were obtained from the base of the tongue to the trachea, while the patient was lying down and breathing quietly with the neck hyperextended. The CT images were filmed on hard copies using both soft tissue and bone window settings in order to better appreciate ossification changes in the laryngeal cartilages. The MRI studies were obtained at 1.5 and 1 T, respectively, using a dedicated surface neck coil mounted to the patient's neck in the supine position. Axial T2-weighted fast-spin-echo (FSE) and axial T1-weighted SE images were obtained from the base of the tongue to the trachea with a scan orientation parallel to the true vocal cords. The image parameters included a slice thickness of 3–4 mm with a 0- to 1-mm intersection

gap. Axial T1-weighted SE images after intravenous administration of gadolinium chelates (0.1 mMol/kg body weight; Magnevist, Schering, Berlin, Germany) were obtained routinely in all patients. Images in the coronal or sagittal plane were obtained additionally after intravenous administration of contrast material in order to better evaluate certain anatomic spaces such as the preepiglottic space in the sagittal plane and the paraglottic space and the ventricle in the coronal plane.

All CT and MRI images were reviewed retrospectively by two radiologists according to predefined criteria. The following structures were evaluated for possible involvement by the tumor: vallecula, epiglottis, preepiglottic space, false cords, aryepiglottic folds, ventricle, paraglottic space, anterior commissure, posterior commissure, true vocal cords, subglottis, thyroid, cricoid and arytenoid cartilages, piriform sinus, retrocricoarytenoid region, posterior pharyngeal wall, esophageal verge, soft tissues of the neck, and lymph nodes. Criteria used for assessment of the primary tumor were the presence of a soft tissue mass or soft tissue thickening, abnormal contrast enhancement, infiltration of fatty tissue, and a combination of these crieria [10–12]. The criteria used for involvement of the laryngeal cartilages at CT included sclerosis, erosion, lysis, and extralaryngeal spread [13]. Because erosion, lysis, and extralaryngeal spread may be considered as specific signs of cartilage invasion [13], they were applied in all three laryngeal cartilages. In addition, sclerosis was used as a sign to detect invasion of the cricoid and arytenoid cartilage because the specificity of this sign has been shown to be moderately high in these two cartilages [13]. However, sclerosis was not considered to be indicative of cartilage invasion in the thyroid cartilage because of its low reported specificity in this cartilage. The presence of sclerosis in the thyroid cartilage was considered to be indicative only of a cartilage abnormality (tumor or peritumoral inflammation) rather than frank invasion. Because the combination of all four CT criteria has a high negative predictive value, the absence of these four signs was considered as a reliable sign to exclude tumor invasion within the laryngeal cartilages [13]. The criteria used for involvement of the laryngeal cartilages at MRI included a decreased signal intensity of the laryngeal cartilage on the T1-weighted SE image associated with an increase in signal intensity on the T2-weighted FSE image and enhancement of the cartilage after administration of contrast material [11, 14–16]. In addition, degree and patterns of contrast enhancement were noted using a three-point scale (slight, moderate, strong) and differentiation between homogenous vs lobulated enhancement (see below) was made. The endolaryngeal and endopharyngeal surface of the tumor was assessed (smooth surface vs rugged surface), as well as the presence or absence of distinct morphologic features such as a stalk, calcifications, or areas of ulceration. The criteria used to assess lymph node metastases included a minimal axial diameter of more than 11 mm in the jugulo-digastric group and of 10 mm elsewhere in the head and neck, grouping of three or more lymph nodes with a minimal axial diameter of 8–9 mm, irregular contrast enhancement, and indistinct nodal margins [17, 18].

Table 1. Atypical forms of squamous cell carcinoma: clinical and endoscopic findings in 31 patients

atypical forms of squamous cell carcinoma	number of patients	mean age (years)	male:female ratio	main symptoms	tumor origin	endoscopic features
undifferentiated carcinoma of nasopharyngeal type	8	67	6:2	dyspnea and palpable lymph nodes	larynx (*n* = 5) hypopharynx (*n* = 3)	intact mucosa[1] intact mucosa[1] (*n* = 2) mucosal lesion[2] (*n* = 1)
verrucous carcinoma	18	55	18:0	hoarseness	larynx	mucosa involved[3]
spindle cell carcinoma	3	66	3:0	dyspnea, episodes of suffocation	larynx (*n* = 2) hypopharynx (*n* = 1)	mucosa involved (*n* = 1)[2] mucosa involved (*n* = 1)[2]
basaloid cell carcinoma	2	56	2:0	dysphagia, pain radiating into the ear	hypopharynx	mucosa involved[2]

[1] submucosal bulge; [2] macroscopic appearance indistinguishable from the common type of squamous cell carcinoma; [3] characteristic appearance at indirect and direct laryngoscopy with filiform projections

Table 2. Atypical forms of squamous cell carcinoma: characteristic radiologic features in 31 patients

atypical forms of squamous cell carcinoma	tumor location	enhancement pattern, morphology	lymph node metastases
undifferentiated carcinoma of nasopharyngeal type	supraglottis, hypopharynx, submucosal location	homogenous enhancement pattern, large tumor mass, no ulceration, no necrosis, no cartilage invasion	yes
verrucous carcinoma	glottis	inhomogenous enhancement, exophytic mass with a rugged surface, limited deep infiltration, rarely cartilage invasion	no
spindle cell carcinoma	supraglottis	inhomogenous enhancement, bulky, ulcerated lesion, thin stalk	variable
basaloid cell carcinoma	piriform sinus and retrocricoarytenoid region	inhomogenous, distinct lobulated enhancement pattern on contrast-enhanced T1-weighted SE images	yes, extranodal spread

The clinical, endoscopic, and histopathologic results were reviewed on the basis of clinical charts, video recordings of endoscopic examinations, and histopathologic slices.

Results

Atypical forms of squamous cell carcinoma included undifferentiated carcinoma of nasopharyngeal type (*n* = 8), verrucous carcinoma (*n* = 18), spindle cell carcinoma (*n* = 3), and basaloid cell carcinoma (*n* = 2). There were 25 laryngeal and 6 hypopharyngeal tumors. Age, gender distribution, main symptoms, and endoscopic appearance are summarized in Table 1.

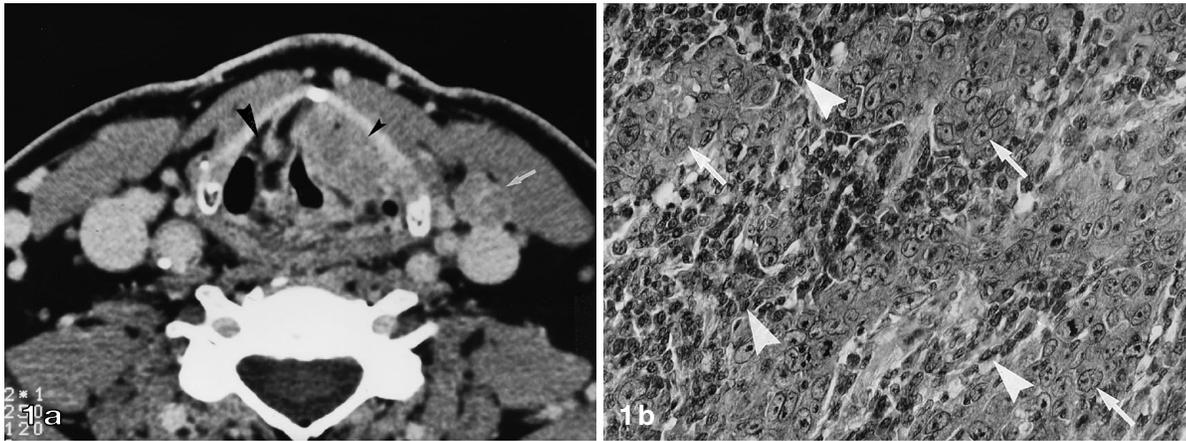### *Undifferentiated carcinoma of nasopharyngeal type*

Clinical and endoscopic findings

Seven of eight patients presented with an intact mucosa at indirect or direct laryngoscopy (Table 1). A submucosal bulge was observed in all patients and initial endoscopic biopsy was negative in all but one patient. Repeat endoscopic biopsies were performed in seven patients on the basis of CT and MRI findings. Computed tomography and MRI not only demonstrated the submucosal extent of the tumor, but also directed the endoscopist to the most appropriate biopsy site. This was of particular importance because, as the mucosa was intact at endoscopy, the mere presence of a solid mass at CT or MRI lead to as many as three repeat endoscopic examinations with deep biopsies in order to obtain the definitive histologic diagnosis (Fig. 1).

Radiologic findings

Computed tomography obtained in six patients demonstrated very large, supraglottic, or piriform sinus masses with homogenous contrast enhancement and without intratumoral necrosis or ulceration (Fig. 1). Magnetic resonance images obtained in three patients displayed similar findings: homogenous, moderately enhancing tumors without areas of necrosis (Fig. 2). The bulk of the

Fig. 1a, b. Undifferentiated carcinoma of nasopharyngeal type: CT appearance. A 73-year-old male patient presenting with increasing dyspnea. Asymmetry of the false cords was seen at endoscopy, suggesting a submucosal left-sided mass. The mucosa appeared, however, intact and endoscopic biopsy was initially negative. **a** Axial, contrast-enhanced CT image at the supraglottic level obtained 10 days after endoscopy demonstrates a large tumor mass in the left false cord with invasion of the paraglottic fat *(small arrowhead)* Note for comparison the appearance of the normal contralateral paraglottic space *(large arrowhead)*. The tumor is adjacent to the left thyroid lamina, which is composed of non-ossified hyaline cartilage. A metastatic lymph node *(arrow)* is seen on the left. The patient underwent three repeat endoscopic biopsies of the left false cord until the definitive histologic diagnosis could be made. **b** High-power micrograph showing cords of large, pale epithelial cells with indistinct cell boundaries and vesicular nuclei *(arrows)* overrun by small lymphocytes *(arrowheads)* characteristic of undifferentiated carcinoma of nasopharyngeal type. Both *arrows* and *arrowheads* point to the nuclei of cells. The patient underwent radiation therapy and is free of recurrence 5.5 years later. (Hematoxylin and eosin staining, original magnification, × 100)

tumor was located within the aryepiglottic fold in seven patients and within the false cord in one patient. In all cases the paraglottic fat was invaded by tumor tissue and invasion of the pre-epiglottic fat was noted in three patients. Transglottic spread was demonstrated at MRI only in one patient. No involvement of the anterior or posterior commissure was observed. Based on CT and MRI findings, none of these tumors displayed neoplastic cartilage invasion despite the large size of the tumor. The endolaryngeal and endopharyngeal tumor surface was smooth. Extensive cervical adenopathy was observed in all patients. The characteristic radiologic features of undifferentiated carcinoma of nasopharyngeal type are summarized in Table 2.

Pathologic findings

Microscopic examination revealed large, poorly differentiated, non-keratinized cells intermingled with lymphocytes. The tumor cells displayed a syncytial appearance with lymphocytes as a reactive non-neoplastic component of the tumor (Fig. 1). Immunocytochemical stains for epithelial membrane antigen and keratin provided further documentation of epithelial differentia-

tion and helped in differentiating the neoplasm from lymphoma.

Verrucous carcinoma

Clinical and endoscopic findings

Endoscopically, all patients presented with cauliflower-like, gray-white tumor masses arising from the glottic level. These masses presented characteristic finger-like projections at endoscopy (Fig. 3). Initial endoscopic biopsy demonstrated verrucous carcinoma in 16 patients and benign adult papillomatosis in 2 patients. Repeat endoscopic biopsies in these two patients finally revealed verrucous carcinoma.
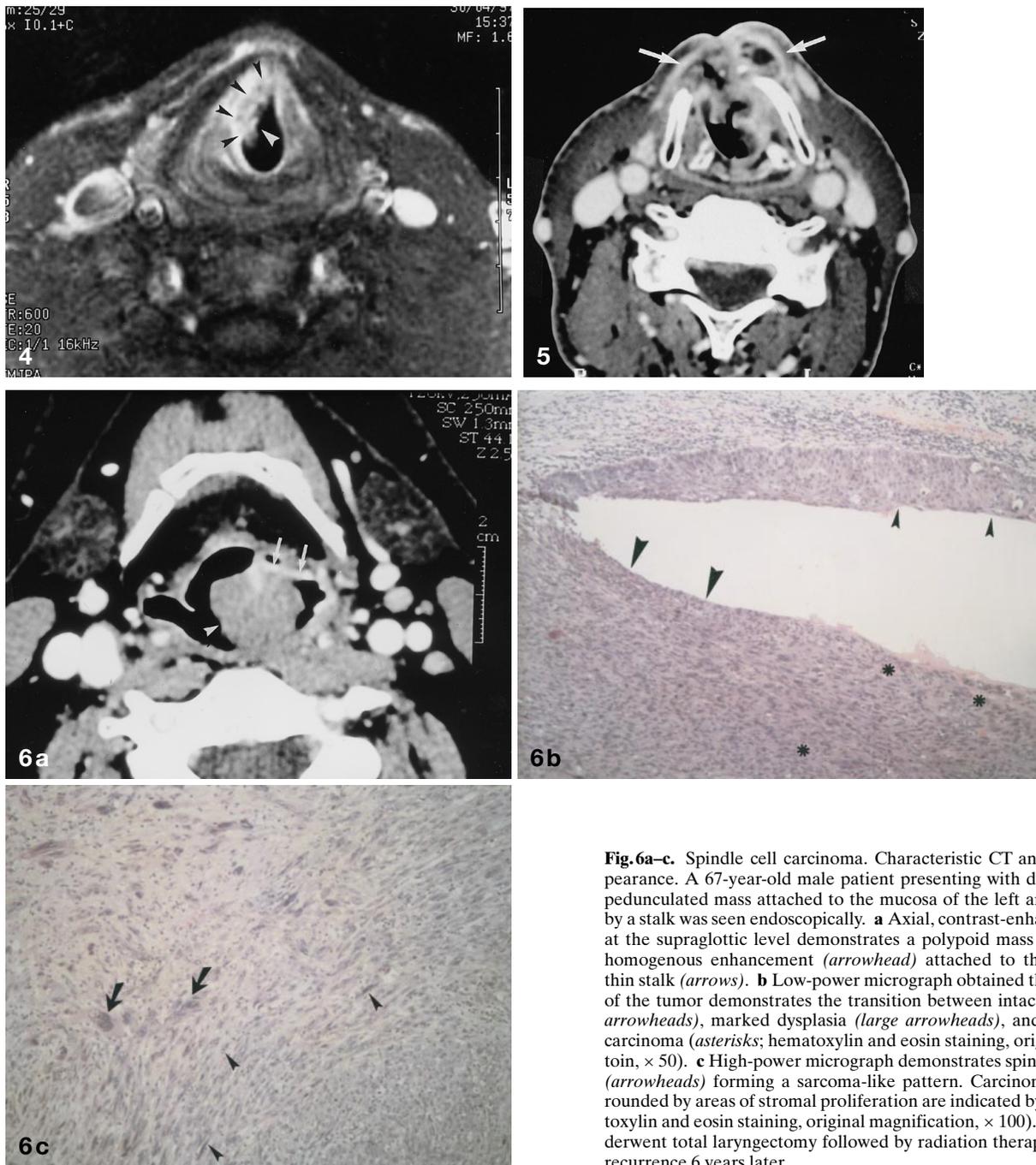
Radiologic findings

In all patients with verrucous carcinoma an exophytic mass arising from one vocal cord with or without involvement of the contralateral cord was seen either at CT (performed in 17 patients) or at MRI (performed in four patients; Figs. 3, 4). The anterior commissure

Fig. 2a–d. Undifferentiated carcinoma of nasopharyngeal type: ▶ MRI appearance. A 76-year-old male patient presenting with multiple palpable neck masses. Endoscopically the right aryepiglottic fold appeared to be thicker than the left aryepiglottic fold and the mucosa was intact. **a** Axial T1-weighted SE image at the supraglottic level. A large tumor mass *(T)* with low signal intensity invades the right aryepiglottic fold *(large arrowhead)* and the paraglottic fat *(small arrowheads)* A large metastatic lymph node is indicated by an *open arrow*. **b** Axial, T2-weighted FSE image at the same level shows a slight increase in signal intensity within the tumor mass and within the metastatic lymph node. **c** Contrast-enhanced, axial T1-weighted SE image demonstrates moderate, homogenous contrast enhancement of the tumor without evidence of intratumoral necrosis. Deep biopsy obtained from beneath the mucosa of the right aryepiglottic fold revealed undifferentiated carcinoma of nasopharyngeal type. The patient underwent total laryngectomy and bilateral neck dissection. **d** Gross surgical specimen viewed from posteriorly and above with the patient's right side oriented to the viewer's right side. Note that the large supraglottic tumor *(arrows)* is covered by an intact mucosa. *E* epiglottis. The patient is free of recurrence 6 years later
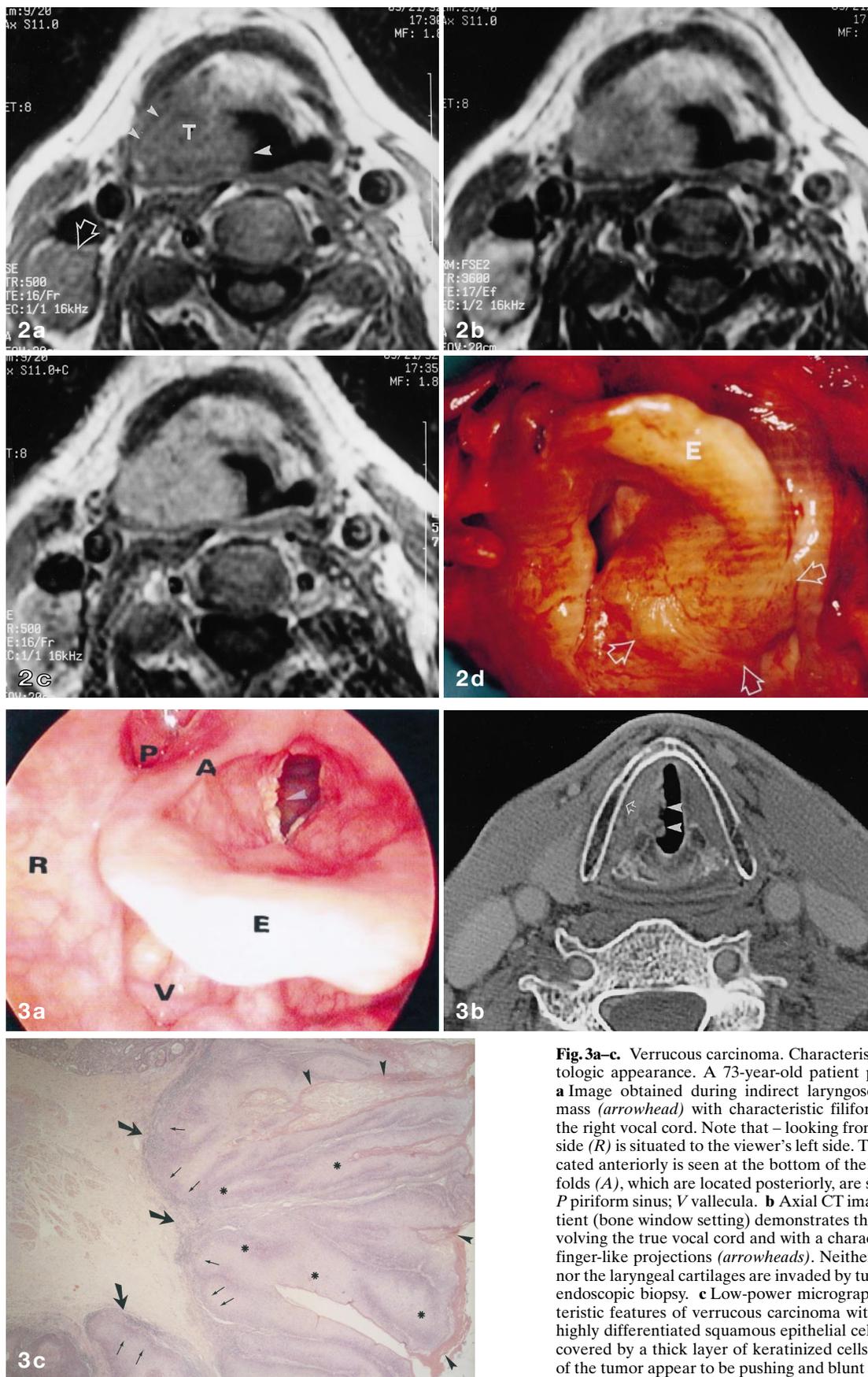
Fig. 3a–c. Verrucous carcinoma. Characteristic endoscopic, CT, and histologic appearance. A 73-year-old patient presenting with hoarseness. **a** Image obtained during indirect laryngoscopy shows a white tumor mass *(arrowhead)* with characteristic filiform projections arising from the right vocal cord. Note that – looking from above – the patient's right side *(R)* is situated to the viewer's left side. The epiglottis *(E)* which is located anteriorly is seen at the bottom of the image and the aryepiglottic folds *(A)*, which are located posteriorly, are seen at the top of the image. *P* piriform sinus; *V* vallecula. **b** Axial CT image obtained in the same patient (bone window setting) demonstrates the right-sided tumor mass involving the true vocal cord and with a characteristic rugged surface with finger-like projections *(arrowheads)*. Neither the paraglottic fat *(arrow)* nor the laryngeal cartilages are invaded by tumor. The patient underwent endoscopic biopsy. **c** Low-power micrograph demonstrates the characteristic features of verrucous carcinoma with long filiform processes of highly differentiated squamous epithelial cells *(asterisks)*. The surface is covered by a thick layer of keratinized cells *(arrowheads)*. The margins of the tumor appear to be pushing and blunt *(thin arrows)* rather than infiltrating. In advance of the tumor margins a severe inflammatory reaction is seen *(thick arrows;* hematoxylin and eosin staining, original magnification, × 50)

Fig. 6a–c. Spindle cell carcinoma. Characteristic CT and histologic appearance. A 67-year-old male patient presenting with dyspnea. A large pedunculated mass attached to the mucosa of the left aryepiglottic fold by a stalk was seen endoscopically. **a** Axial, contrast-enhanced CT image at the supraglottic level demonstrates a polypoid mass with moderate, homogenous enhancement *(arrowhead)* attached to the mucosa by a thin stalk *(arrows)*. **b** Low-power micrograph obtained through the stalk of the tumor demonstrates the transition between intact mucosa *(small arrowheads)*, marked dysplasia *(large arrowheads)*, and squamous cell carcinoma *(asterisks*; hematoxylin and eosin staining, original magnificatoin, × 50). **c** High-power micrograph demonstrates spindle-shaped cells *(arrowheads)* forming a sarcoma-like pattern. Carcinomatous foci surrounded by areas of stromal proliferation are indicated by *arrows* (hematoxylin and eosin staining, original magnification, × 100). The patient underwent total laryngectomy followed by radiation therapy and is free of recurrence 6 years later

Fig. 4. Verrucous carcinoma. Characteristic MRI appearance. Contrast-enhanced, fat-saturated T1-weighted SE image at the level of the subglottis shows an exophytic tumor mass with a rugged surface *(white arrowhead)*. The tumor mass enhances only moderately. *Black arrowheads* point to the blunt tumor margins. Note the very strong enhancement observed in immediate vicinity of the tumor caused by a severe inflammatory reaction. These findings were confirmed histologically (see Fig. 3 c for comparison)

Fig. 5. Advanced verrucous carcinoma with massive destruction of the laryngeal skeleton. Axial, contrast-enhanced CT image obtained in a 63-year-old male patient with verrucous carcinoma of the larynx. A large tumor mass with massive destruction of the thyroid cartilage and extension into the soft tissues of the neck *(arrows)* is seen. Note that despite the unusual finding of laryngeal cartilage invasion, which is uncommonly seen in verrucous carcinoma, the tumor presents a characteristic rugged surface with deep finger-like projections. The patient underwent total laryngectomy and histology confirmed the radiologic findings

was involved in four patients and the laryngeal ventricle was involved in three cases. In 13 patients the tumor involved the glottic level alone, in 3 patients the tumor involved the glottic and supraglottic level, and in 2 patients the tumor involved the glottic and subglottic level (Figs. 4, 5). In addition to a frankly exophitic mass, 11 of the 18 tumors in our series displayed a rugged surface with filiform projections either at CT or at MRI (Figs. 3–5). In seven cases an exophitic mass without filiform projections was identified at imaging, whereas endoscopy clearly showed the characteristic filiform projections. Extensive submucosal tumor spread was not observed at initial presentation in 16 cases and invasion of the paraglottic fat was seen only

in 2 cases. Infiltration of the laryngeal cartilages was uncommon and was observed only in two cases (one thyroid and one arytenoid cartilage; Fig. 5). The signal intensity patterns on the different pulse sequences and the enhancement pattern after administration of contrast material were similar to those observed in the common type of squamous cell cancer, i.e., low signal intensity on the T1-weighted SE image, slightly increased signal intensity on the T2- weighted FSE image, and slight to moderate enhancement after administration of contrast material. However, the moderately enhancing tumor mass was surrounded by strongly enhancing tissue (Fig. 4), and comparison with histopathology revealed that this strongly enhancing tissue corresponded to peritumoral inflammation (see also Fig. 3c). None of our 18 patients with verrucous carcinoma displayed lymph node metastases at cross-sectional imaging. The characteristic radiologic features seen in verrucous carcinoma are summarized in Table 2.

Pathologic findings

The tumors were composed of islands and solid cords of highly differentiated squamous epithelial cells (Fig. 3). Cytologic criteria of malignancy were lacking or were minimal. Mitoses were rare and tended to be concentrated in the basal- and parabasal regions. Deeply projecting, cleft-like, filiform spaces with degenerating keratin, advancing, pushing and well-demarcated margins, as well as prominent stromal evidence of a chronic inflammatory reaction (Fig. 3), were characteristic histologic features.

Spindle cell carcinoma

Clinical and endoscopic findings

Endoscopically, the tumor originated either from the supraglottis or from the medial wall of the piriform sinus. The mucosa overlying the pedunculated tumor was macroscopically indistinguishable from the mucosa seen in the common type of squamous cell cancer. However, a characteristic tumor stalk could be identified endoscopically in two cases. The surface of the tumor was ulcerated in two patients.

Radiologic findings

Computed tomography obtained in three patients with spindle cell carcinoma demonstrated large, exophytic, pedunculated masses arising from the supraglottic region or piriform sinus with inhomogenous, moderate contrast enhancement, without invasion of the laryngeal cartilages and with a characteristic stalk (Fig. 6). Cervical lymph node metastases were observed in one patient. The characteristic radiologic features are summarized in Table 2.

Pathologic findings

Characteristic histologic findings were spindle-shaped cells forming a sarcoma-like pattern and atypical, bizarre cells with pleomorphic nuclei. Areas of more or less differentiated squamous cell carcinoma, in situ, infiltrative, or both, were found next to apparently sarcomatous areas (Fig. 6). Carcinomatous foci were also found within the central areas of stromal proliferation (Fig. 6). Immunocytochemical investigations to identify keratin intermediate filaments were helpful in establishing the diagnosis. Lymph nodes metastases seen in one patient contained both a squamous and a spindle cell element.

Basaloid cell carcinoma

Clinical and endoscopic findings

Both patients with basaloid cell carcinoma of the hypopharynx demonstrated large masses arising from the medial wall of the piriform sinus extending into the retrocricoarytenoid region at endoscopy. The macroscopic aspect of the tumor was indistinguishable from the common form of squamous cell cancer; however, initial endoscopic biopsy revealed the correct diagnosis in both cases.

Radiologic findings

Magnetic resonance imaging obtained in our patients with basaloid cell carcinoma of the hypopharynx demonstrated large masses involving the medial wall of the piriform sinus, the retrocricoarytenoid region, the paraglottic fat, and the esophageal verge. The laryngeal cartilages were not involved. A distinct "lobulated" enhancement pattern was observed on contrast-enhanced T1-weighted SE images (Fig. 7). Based on our own experience, we have not observed this lobulated enhancement pattern in the common form of squamous cell carcinoma, which typically shows a relatively homogenous enhancement with or without associated areas of ulceration or necrosis (Fig. 8). Cervical lymph node metastases with signs of extracapsular spread were present in both patients with basaloid cell carcinoma. The characteristic radiologic features are summarized in Table 2.

Pathologic findings

As both patients underwent total laryngectomy with unilateral neck dissection, histologic analysis confirmed all MRI findings with respect to involvement of the aforementioned structures. Characteristic histologic findings were a basaloid pattern associated with in situ or invasive squamous cell carcinoma. The tumor consisted of small crowded cells with hyperchromatic nuclei and scant cytoplasm and areas of coagulative necrosis within the central areas of the tumor lobules (come-
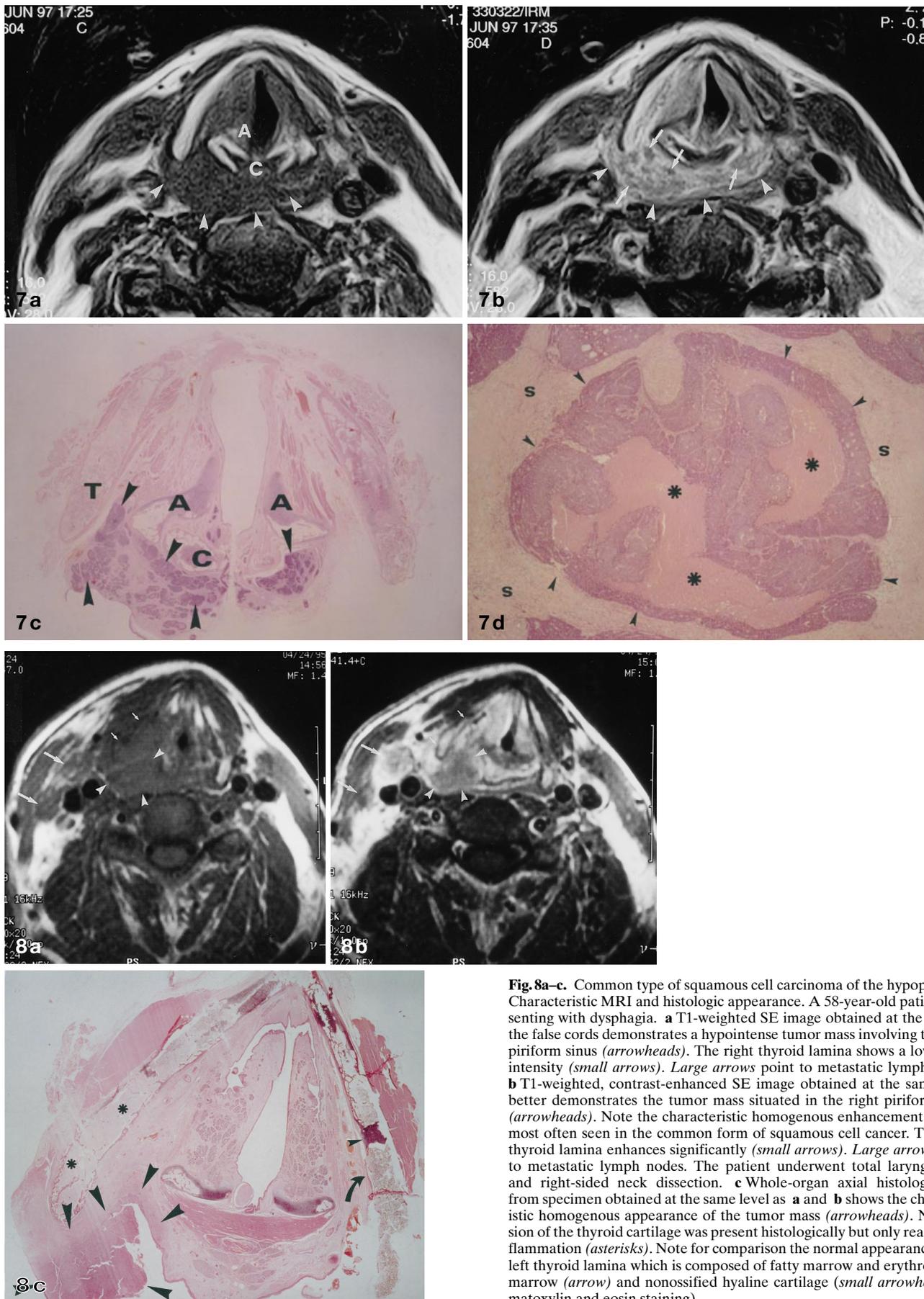
Fig. 8a–c. Common type of squamous cell carcinoma of the hypopharynx. Characteristic MRI and histologic appearance. A 58-year-old patient presenting with dysphagia. **a** T1-weighted SE image obtained at the level of the false cords demonstrates a hypointense tumor mass involving the right piriform sinus *(arrowheads)*. The right thyroid lamina shows a low signal intensity *(small arrows)*. *Large arrows* point to metastatic lymph nodes. **b** T1-weighted, contrast-enhanced SE image obtained at the same level better demonstrates the tumor mass situated in the right piriform sinus *(arrowheads)*. Note the characteristic homogenous enhancement pattern most often seen in the common form of squamous cell cancer. The right thyroid lamina enhances significantly *(small arrows)*. *Large arrows* point to metastatic lymph nodes. The patient underwent total laryngectomy and right-sided neck dissection. **c** Whole-organ axial histologic slice from specimen obtained at the same level as **a** and **b** shows the characteristic homogenous appearance of the tumor mass *(arrowheads)*. No invasion of the thyroid cartilage was present histologically but only reactive inflammation *(asterisks)*. Note for comparison the normal appearance of the left thyroid lamina which is composed of fatty marrow and erythropoietic marrow *(arrow)* and nonossified hyaline cartilage (*small arrowhead*; hematoxylin and eosin staining)

◄ **Fig. 7a–d.** Basaloid cell carcinoma of the hypopharynx. Characteristic MRI and histologic appeearance. A 64-year-old patient presenting with pain and dysphagia. **a** T1-weighted SE image obtained at the level of the true vocal cords demonstrates a tumor mass involving the right piriform sinus and the retrocricoarytenoid region *(arrowheads)*. The right thyroid lamina has high signal intensity due to the presence of fatty marrow. *C* cricoid cartilage; *A* right arytenoid cartilage. **b** T1-weighted, contrast-enhanced SE image obtained at the same level better demonstrates the tumor mass situated in the right piriform sinus and retrocricoarytenoid region *(arrowheads)*. Note the distinct lobulated enhancement pattern seen in this type of tumor. The tumor lobules *(white arrows)* display moderate enhancement after administration of contrast material while the stroma surrounding the tumor lobules enhances significantly. The patient underwent total laryngectomy and right-sided neck dissection. **c** Whole-organ axial histologic slice from specimen obtained at the same level as **a** and **b** shows the characteristic tumor lobules *(arrowheads)* which are surrounded by a reactive stroma. Hematoxylin and eosin staining. *C* cricoid cartilage; *A* arytenoid cartilages; *T* right thyroid lamina with normal fatty marrow. None of the laryngeal cartilages were invaded histologically. **d** Detail from the same slice shows a tumor lobule *(arrowheads)* consisting of small cells with hyperchromatic nuclei and areas of coagulative necrosis *(asterisks)* within the central area of the tumor lobule. *S* stroma between tumor lobules. (Hematoxylin and eosin staining, original magnification, × 50)

donecrosis; Fig. 7). Small cystic spaces with a material resembling mucin as well as focal areas of hyalinization were additional histologic findings.

Discussion

Atypical forms of squamous cell carcinoma of the larynx and hypopharynx constitute a distinct histopathologic and clinical entity. Some of these unusual tumors are located mainly beneath an intact mucosa and must therefore be considered as a diagnostic challenge to the endoscopist. Because of their different prognostic and therapeutic implications, atypical forms of squamous cell carcinoma must not only be carefully distinguished from typical squamous cell carcinoma, but also from other neoplasms that may involve primarily the submucosal compartment of the larynx, such as chondrosarcoma, lymphoreticular and lipomatous tumors, tumors of the minor salivary glands, and vasoformative tumors [9].

Undifferentiated carcinoma of nasopharyngeal type is an unusual variant of squamous cell carcinoma with a distinct lymphoid component [19–23]. Synonyms used in the literature for this tumor include lymphoepithelial carcinoma, undifferentiated carcinoma of nasopharyngeal type, and lymphoepithelioma. Although acccording to Micheau et al. [19] this neoplasm accounts for 0.2 % of all laryngeal cancers, less than 20 cases have been reported to date [1, 19–23]. The tumor affects mainly men between 50 and 70 years of age; in our series six of eight patients with this tumor type were males. Infection with the Epstein-Barr virus (EBV) appears to play an important etiologic role. The tumor most commonly arises in the supraglottic region because these regions are very rich in lymphatic tissue. Seven of eight patients with this type of tumor presented with supra-

glottic or piriform sinus masses covered by an intact mucosa at endoscopic examination (Figs. 1, 2; Table 1). Since the tumor is deep seated, biopsies must be obtained from beneath the mucosa or the lesion will be missed (Fig. 1). Therefore, multiple biopsies may be necessary until the correct histologic diagnosis can be made. Undifferentiated carcinoma of nasopharyngeal type often metastasizes to the cervical lymph nodes and sometimes to the lungs or other organs, and cervical lymph node metastases may be the first presenting symptom [21–23]. In our series, all patients with this tumor type presented with lymph node metastases that were detected either by palpation or by cross-sectional imaging studies. Because only few cases of undifferentiated carcinoma of nasopharyngeal type have been reported in the larynx and hypopharynx, no final conclusion as to prognosis and therapy is possible. Radiotherapy alone or in combination with chemotherapy appears to be effective in eradicating localized disease [1, 20, 21]. Based on the observations of this series, the most striking feature in this particular tumor type was the discrepancy between an intact mucosa at endoscopy and a solid mass having similar imaging features as the common form of squamous cell carcinoma. Interestingly, despite the large size of the tumor mass and widespread invasion of the paraglottic space, no cartilage invasion was seen at cross-sectional imaging. In addition, CT and MRI detected lymph node metastases in all patients, leading us to suspect squamous cell cancer as the most likely diagnosis. A few authors have pointed out that squamous cell carcinoma may be located beneath an intact laryngeal or hypopharyngeal mucosa [7, 8, 24]. Squamous cell carcinoma found entirely beneath an intact laryngeal mucosa is thought to arise from the apex of the laryngeal ventricle. A tumor that arises on the mucosa of the apex of the laryngeal ventricle can easily be hidden from the endoscopist's view by the overhanging false cord [7, 24]. Due to the vicinity of the laryngeal ventricle to the paraglottic space, tumors may easily gain access to the paraglottic space and present endoscopically as a submucosal bulge. Although important to recognize, purely submucosal squamous cell cancers are uncommon. In our series all purely submucosal squamous cell cancers were undifferentiated carcinomas of nasopharyngeal type. Because in most published series the exact histologic characterization of submucosal squamous cell cancers of the larynx has not been specified, it is impossible to determine whether or not previously published cases belong to the same tumor type as observed in our series.

Verrucous carcinoma or Ackerman tumor is a distinct pathological variant of well-differentiated squamous cell carcinoma with a reported incidence of 1–4 % of all laryngeal cancers [25]. It must not be confused with the common form of squamous cell carcinoma, because it differs both in structural characteristics and prognosis, which is excellent when adequate treatment is adopted from the beginning. Glanz and Kleinsasser consider this lesion benign, and propose the term "verrucous acanthosis," classifying such lesions as facultative precanceroses [26]. The recently revised

WHO classification, however, classifies the verrucous carcinoma as a distinct malignat tumor [1]. It occurs predominantly in men in their seventies and eighties and presents clinically as a warty, bulky outgrowth with multiple filiform projections usually affecting one vocal cord (Fig. 3). Viral infection with the human papilloma virus (HPV) type 16 appears to play an important etiologic role [27]. Verrucous carcinoma of the larynx almost never metastasizes to the lymph nodes [25, 26, 28, 29]. Considerable controversy exists as to the correct treatment for this tumor [1–5, 25–31]. A recurrence rate of 51–71 % after radiation therapy has been reported as opposed to only 7 % recurrence rate after surgery [25, 26]. In addition, several authors have reported a high risk of post-irradiation anaplastic or sarcomatoid changes, the latent period for anaplastic transformation being as short as a few months [28, 29]. This very short transformation time may be explained by the fact that verrucous carcinoma cells are already genetically abnormal [29]. Evidence of increased metastatic potential after irradiation of T1–T2 verrucous carcinoma of the larynx as compared with the common type of squamous cell carcinoma has been provided by some groups [30]. Surgery alone is therefore considered in most centers as the treatment of choice, and in most cases the lesion is amenable to conservative surgery (cordectomy, partial voice-preserving laryngectomy) [1–4, 25–31]. Because cervical and distant metastases have not been reported in non-irradiated verrucous carcinoma, operative treatment typically does not include neck dissection [1]. Because superficial biopsies may lack the characteristic histologic signs, full-thickness biopsies or, when possible, excisional biopsy are necessary to establish the diagnosis [5, 31]. As suggested by several authors, multiple biopsies may be necessary to establish the diagnosis when a clinically malignant-appearing lesion contradicts a benign histologic appearance [5, 31]. In two patients initial histologic evaluation failed to provide the correct diagnosis because the biopsy sample was too superficial, and only repeat deep biopsy revealed the correct diagnosis. The radiologic aspect may be of additional help not only in suggesting a diagnosis other than the common form of squamous cell cancer, but also in insisting to perform additional biopsies so as to obtain the definitive, correct histologic diagnosis. Based on the findings of this series, verrucous carcinoma may display a characteristic radiologic aspect: an exophytic mass with a rugged surface and finger-like, deep projections, limited deep tumor infiltration, moderate enhancement after administration of contrast material, and absence of lymph node metastases (Table 2). Although a rugged tumor surface with inframilimetric, finger-like intraluminal projections appeared as a characteristic feature on both direct laryngoscopy and histologic analysis, these features were only identified at cross-sectional imaging in 11 of 18 patients. In the other seven patients the surface of the exophytic tumor appeared relatively smooth at both CT and MRI. This may be explained by the slice thickness used in this study (1.5–3 mm with CT and 3–4 mm with MRI).

Spindle cell carcinoma is a rare biphasic variant of squamous cell carcinoma in which a pseudosarcomatous component dominates the microscopic appearance of the tumor. Various synonymous terms have been used to designate this tumor including spindle cell squamous carcinoma, pseudosarcoma, pleomorphic carcinoma, Lane tumor, polypoid carcinoma, biphasic spindle cell carcinoma, etc. [32–35]. The larynx is the most common site, followed by the oral cavity and esophagus [1, 5, 32–35]. The incidence varies between 0.5 and 1 % of all malignant laryngeal neoplasms. Although these tumors have the same age and gender predilection as the common type of squamous cell carcinoma, most spindle cell carcinomas have been reported to have a highly exophytic, polypoid shape. The tumor arises predominantly from the supraglottic region. According to the literature, two thirds of the tumors present endoscopically as pedunculated masses attached to the mucosa by a stalk, whereas one third of the lesions present as sessile or infiltrating masses. In all of our patients with spindle cell carcinoma the tumor originated in the supraglottis or piriform sinus and was attached to the mucosa by a stalk. The treatment of choice is surgery and neck dissection is often indicated. However, radiotherapy has also been used successfully in limited lesions. Patients with polypoid tumors appear to have a better prognosis than patients with infiltrating tumors and survival appears to be inversly related to the depth of invasion [32, 33]. As with other atypical forms of squamous cell carcinoma, large biopsies are often necessary to establish the correct diagnosis because superficial biopsies may lack the characteristic histologic signs [35]. Based on the findings of this series, spindle cell carcinoma may display a characteristic radiologic aspect: large, exophytic, pedunculated masses arising from the supraglottic region or piriform sinus with inhomogenous contrast enhancement and with a thin stalk (Fig. 6; Table 2). Due to the small number of cases of spindle cell cancer in this series, further studies are necessary to confirm whether or not these diagnostic findings may be considered as characteristic.

Basaloid squamous cell carcinoma (also called basaloid cell carcinoma) is a rare, distinct histopathological entity with a mixed basaloid and squamous component [1, 36–39]. It is believed to arise from a pluripotent primitive cell located at the base of the pseudostratified columnar epithelium. The predilection sites are the supraglottic larynx, hypopharynx, and base of the tongue. The prognosis is usually worse than that of the common type of squamous cell carcinoma. The tumor is therefore regarded as a high-grade malignancy with a tendency for locally aggressive behavior and early regional and distant metastases [36–39]. The most common sites of metastatic spread are the cervical lymph nodes followed by the lung, bone, and skin. The treatment of choice is surgery followed by radiation therapy. Because of a high incidence of distant metastases, some authors have suggested additional adjuvant chemotherapy [39]. As with other atypical forms of squamous cell carcinoma, multiple biopsies may be necessary to establish the correct definitive histologic diagnosis because biopsy

specimens may very often not be representative for the entire lesion [38]. The tumor may be confused histologically with adenoid cystic carcinoma, adenosquamous carcinoma, or squamous cell carcinoma. Metastases to the lymph nodes may reveal both the squamous and the basaloid component or only one of the two tumor components. In both of our patients with basaloid cell carcinoma, metastatic adenopathy with signs of extracapsular spread and carcinomatous lymphangitis were seen histologically. The most striking radiologic feature observed in this particular tumor type was the distinct lobulated enhancement pattern (Fig. 7), which we have not encountered in the common form of squamous cell cancer. This lobulated enhancement pattern corresponded to the macroscopic architecture of the tumor which consists of tumor lobules dispersed within and surrounded by a fibrovascular stroma. Although this enhancement pattern observed on contrast-enhanced T1-weighted SE sequences may turn out to be characteristic for basaloid cell carcinoma, further studies involving a larger patient population are required.

In summary, our study indicates that although the MR and CT features of atypical forms of squamous cell carcinoma cannot be considered pathognomonic, they may still be characteristic and should raise the differential diagnosis even if endoscopic biopsy has been negative or nonspecific. Further endoscopic work-up with deep biopsies at the appropriate site are warranted because this may influence prognosis and treatment.

References

1. Ferlito A (1993) Atypical forms of squamous cell carcinoma. In: Ferlito A (ed) Neoplasms of the larynx. Churchill Livingstone. Edinburgh, pp 135–167
2. Hyams VJ, Batsakis JG, Michaels L (1988) Tumors of the upper respiratory tract and ear. In: Hartmann WH, Sobin LH (eds) Atlas of tumor pathology, second series, fasc. 25. Armed Forces Institute of Pathology, Washington DC
3. Curtin HD (1996) The larynx. In: Som PM, Curtin HD (eds) Head and neck imaging, 3rd edn. Mosby, St. Louis, pp 612–707
4. Kleinsasser O (1988) Tumors of the larynx and hypopharynx. Thieme, New York, pp 1–349
5. Batsakis JG (1979) Tumors of the head and neck. Clinical and pathologic considerations, 2nd edn. Williams and Wilkins, Baltimore, pp 1–563
6. Mancuso AA, Hanafee WN (1983) Elusive head and neck carcinomas beneath intact mucosa. Laryngoscope 93: 133–139
7. Saleh EM, Mancuso AA, Stringer SP (1992) CT of submucosal and occult laryngeal masses. J Comput Assist Tomogr 16: 87–93
8. Foer B de, Hermans R, Van der Goten A, Delaere PR, Baert AL (1997) Imaging features in 35 cases of submucosal laryngeal mass lesions. Eur Radiol 6: 913–916
9. Becker M, Moulin G, Kurt AM et al. (1998) Non-squamous cell neoplasms of the larynx: radiologic–pathologic correlation. Radiographics 18: 1189–1209
10. Hermans R, Van der Goten A, Baert AL (1997) Image interpretation in CT of laryngeal carcinoma: a study of intra- and interobserver reproducibility. Eur Radiol 7: 1086–1090
11. Zbären P, Becker M, Laeng H (1996) Pretherapeutic staging of laryngeal cancer: clinical findings, computed tomography and magnetic resonance imaging versus histopathology. Cancer 77: 1263–1273
12. Becker M, Hasso AN (1996) Imaging of malignant neoplasms of the pharynx and larynx. In: Taveras JM, Ferruci JT (eds) Radiology: diagnosis–imaging–intervention. Lippincott, pp 1–16
13. Becker M, Zbären P, Delavelle J et al. (1997) Neoplastic invasion of the laryngeal cartilage: reassessment of criteria for diagnosis at CT. Radiology 203: 521–532
14. Castelijns JA, Gerritsen GJ, Kaiser MC et al. (1988) Invasion of laryngeal cartilage by cancer: comparison of CT and MR imaging. Radiology 167: 199–206
15. Becker M, Zbären P, Laeng H et al. (1995) Neoplastic invasion of the laryngeal cartilage: comparison of MR imaging and CT with histopathologic correlation. Radiology 194: 661–669
16. Castelijns JA, Becker M, Hermans R (1996) The impact of cartilage invasion on treatment and prognosis of laryngeal cancer. Eur Radiol 6: 156–169
17. van den Brekel MWM, Stel HV, Castelijns JA et al. (1990) Cervical lymph node metastasis: assessment of radiologic criteria. Radiology 177: 379–384
18. Som PM (1996) Lymph nodes. In: Som PM, Curtin HD (eds) Head and neck imaging, 3rd edn. Mosby, St. Louis, pp 772–794
19. Micheau C, Luboinski B, Schwaab G, Richard J, Cachin Y (1979) Lymphoepitheliomas of the larynx (undifferentiated carcinomas of nasopharyngeal type. Clin Otolaryngol 4: 43–48
20. Toker C, Peterson DW (1978) Lymphoepithelioma of the vocal cord. Arch Otolaryngol 104: 161–162
21. Shanmugaratnam K, Chan S, De-The G et al. (1979) Histopathology of nasopharyngeal carcinoma: correlations with epidemiology, survival rates and other biological characteristics. Cancer 44: 1029
22. Stanley RJ, Weiland LH, DeSanto LW, Neel HB III (1985) Lymphoepithelioma (undifferentiated carcinoma) of the laryngohypopharynx. Laryngoscope 95: 1077–1081
23. Ferlito A (1977) Primary lymphoepithelial carcinoma of the hypopharynx. J Laryngol Otol 91: 361–367
24. Kirchner JA (1984) Pathways and pitfalls in partial laryngectomy. Ann Otorhinolaryngol 93: 301–305
25. Ferlito A, Recher G (1980) Ackerman's tumor (verrucous carcinoma) of the larynx. A clinicopathologic study of 77 cases. Cancer 46 1617–1630
26. Glanz H, Kleinsasser O (1987) Verrucous carcinoma of the larynx: a misnomer. Arch Otorhinolaryngol 244: 108–111
27. Brandsma JL, Steinberg BM, Abramson AL, Winkler B (1986) Presence of human papilloma virus type 16 related sequences in verrucous carcinoma of the larynx. Cancer Res 46: 2185–2188
28. Demian SDE, Bushkin FL, Echevarria RA (1973) Perineural invasion and anaplastic transformation of verrucous carcinoma. Cancer 32: 395–401
29. Abramson AL, Brandsma J, Steinberg B, Winkler B (1985) Verrucous carcinoma of the larynx. Arch Otolaryngol 111: 709–715
30. Edström S, Johansen SL, Lindström J, Sandin I (1987) Verrucous squamous cell carcinoma of the larynx: evidence for increased metastatic potential after irradiation. Otolaryngol Head Neck Surg 97: 381–384
31. Ibekwe AO, Duwall E (1988) Verrucous carcinoma of the larynx: problems in diagnosis and treatment. J Laryngol Otol 102: 79–82
32. Weidner N (1987) Sarcomatoid carcinoma of the upper aerodigestive tract. Sem Pathol 4: 157–168
33. Hellquist H, OLofson J (1989) Spindle cell carcinoma of the larynx. APMIS 97: 1103–1113
34. Brodsky G (1984) Carcino (pseudo)sarcoma of the larynx: the controversy continues. Otolaryngol Head Neck Surg 17: 185–197
35. Leventon GS, Evans HL (1970) Sarcomatoid squamous cell carcinoma of the mucous membranes of the head and neck: a clinicopathologic study of 20 cases. Cancer 26: 1311–1320
36. Wain SL, Kier R, Vollmer RT, Bossen EH (1986) Basaloid-squamous carcinoma of the tongue, hypopharynx and larynx: report of 10 cases. Hum Pathol 17: 1158–1166
37. Batsakis JG, El Naggar A (1989) Basaloid–squamous cell carcinomas of the upper aerodigestive tract. Ann Otol Rhinol Laryngol 98: 919–920
38. Banks ER, Frieson HF Jr, Mills SE, George E, Zarbo RJ, Swanson PE (1992) Basaloid–squamous cell carcinoma of the head and neck. A clinicopathologic and immunohistochemical study of 40 cases. Am J Surg Pathol 16: 939–946
39. McKay MJ, Bilous AM (1989) Basaloid–squamous carcinoma of the hypopharynx. Cancer 63: 2528–2531