32

Advances in Oto-Rhino-Laryngology
Editor: C. R. Pfaltz

New Aspects of Fundamental Problems in Laryngology and Otology

Editor: C. R. Pfaltz

New Aspects of Fundamental Problems in Laryngology and Otology

Volume Editor
C.R. Pfaltz, Basel

103 figures and 10 tables, 1984

S. Karger · Basel · München · Paris · London · New York · Tokyo · Sydney

Advances in Oto-Rhino-Laryngology

National Library of Medicine, Cataloging in Publication
New aspects of fundamental problems in laryngology and otology
Volume editor, C.R. Pfaltz. – Basel; New York: Karger, 1984.
(Advances in oto-rhino-laryngology; v. 32)
1. Laryngeal Neoplasms 2. Carcinoma, Squamous Cell 3. Facial Nerve – anatomy & histology 4. Facial Nerve Diseases I. Pfaltz, C.R. (Carl Rudolf) II. Series
WI AD 701 v.32 [WV 520 N532]
ISBN 3–8055–3701–8

Printed in Switzerland by Thür AG Offsetdruck, Pratteln
ISBN 3–8055–3701–8

Contents

Facial Nerve Disorders: Anatomical, Histological and Clinical Aspects

Adv. Oto-Rhino-Laryng., vol. 32, pp. 1–123 (Karger, Basel 1984)

Carcinoma of the Larynx

Growth, p-Classification and Grading of Squamous Cell Carcinoma of the Vocal Cords

Hiltrud K. Glanz

Dept. of Otolaryngology, Head and Neck Surgery (Chairman: Prof. *O. Kleinsasser*), Philipps University, Marburg (Lahn), FRG

Contents

Preface[1]

As a long-time student of the behavior of laryngeal cancer, I was delighted to discover this carefully prepared and meticulously documented study of the disease as it arises in various parts of the human larynx. Dr. *Glanz'* report extends our understanding of the subject into a new dimension.

Previous studies have usually been based on celloidin sections, which are about 20 µm thick and so do not permit the kind of detailed study of cellular anatomy that the researcher often needs. By contrast, Dr. *Glanz'* sections are prepared in Paraplast at 6–8 µm thickness, and demonstrate such important features as the junctional areas between squamous and ciliated epithelium, squamous metaplasia, adjacent areas of carcinoma in situ, and the type of cellular infiltrate adjacent to areas of squamous cell carcinoma. These fine details are readily apparent in Dr. *Glanz'* histological preparations, while other, less subtle features of the tumor's biological behavior such as invasion of the laryngeal framework, spread of tumor under intact mucosa and early infiltration of perichondrium are easily identified.

[1] Preface by John A. Kirchner, MD, Professor of Otolaryngology, Yale University, New Haven, Conn. (USA).

A 'malignancy index' is proposed, and is based on four features that are easily recognizable in surgical specimens. These include: degree of cellular differentiation, peripheral growth pattern, vascular invasion and lymphatic response. Each feature is assigned a numerical value, the total of which represents the malignancy index. The higher the index, the worse the prognosis, regardless of the size of the tumor or the type of treatment.

Dr. *Glanz* has performed a valuable service to laryngology by organizing her material in a clear and concise manner, and by making her observations available to a wider audience by this excellent English translation. It should be carefully studied by every laryngologist.

Introduction: Aims of the Study

The adequate treatment of laryngeal carcinomas requires an exact knowledge of their development and spread and their immunological reactions evoked in the patient. The following analysis refers to 108 specimens of surgically excised vocal cord cancers the spontaneous growths of which not having been affected by a preceding therapy. Their 3-dimensional extension is demonstrated by subserial sections, and the relationship between their intra- and submucous spread is illustrated by isomorphic epithelial regions.

Frequently occurring, characteristic patterns of tumour spread are pointed out according to which most vocal cord cancers can be associated to special types. Particular details of tumour development in the laryngeal regions are separately examined.

The results raise the question whether the prevailing classification of laryngeal cancer into three regions can be any longer considered to be appropriate. Moreover, they show the difference between the extension of the tumours assessed preoperatively according to the rules of the TNM-system and their actual extension established after serial sections: they differ in more than 50%. Therefore, a pathohistological staging system (p-classification) has been conceived and introduced.

In its second part the study describes the histomorphological features of malignant tumours and proposes a 'grading system' based upon revised histological parameters. They are correlated to the clinical follow-up, especially to the incidence of regional metastases. This system helps calculate the dynamics in the growth of each individual cancer by using a malignancy index.

Material and Methods

Clinical Data

From April 1973 to March 1978, 205 squamous cell carcinomas of the larynx and hypopharynx were diagnosed and treated at the Marburg University ENT Clinic. 144 (70%) of these tumours originated from the glottic region, 45 (22%) from the supraglottic region including the marginal zone, and 16 (8%) from the hypopharynx.

108 carcinomas of the vocal cords including those spreading to the sub- and supraglottic regions received primary surgery. Their specimens were investigated by subserial sections.

Age Distribution (fig. 1). Most of the 144 patients with vocal cord cancer were between 55 and 75 years old; the youngest of them was 41, the oldest 88 years old. 9 (25%) patients were females and, on average, 10 years younger than the male ones.

History. About 94% of the patients were smokers, 2 males and 6 females were not. The non-smokers suffered only from early vocal cord cancer or carcinoma in situ. Exact data concerning the consumption of alcohol were not available; excessive drinking was generally denied.

The comparatively high number of lumbermen was remarkable; this high incidence may be due to the fact that the Marburg ENT Clinic is surrounded by wide forests. Other aetiologic factors, e.g. exposition of patients to asbestos or other cancerogenic chemical agents, correlated to vocal cord cancer could not be observed.

Patients suffered from hoarseness and/or airway obstruction for 4 weeks to 2 years before assessment.

Assessment of Diagnosis. After indirect laryngoscopy microlaryngoscopy was performed in each case in order to investigate the nature and the size of the lesion and to take a biopsy. In suspected submucous spread tomograms of the larynx were made. The preoperative TNM classification was applied according to certainty factors 2 and 5 [220].

Clinical Management. 58 out of 108 patients with vocal cord cancer were treated by partial resection of the larynx: endolaryngeal excisions (7 cases), partial or total cordectomy after thyrotomy (35 cases), modified hemilaryngectomies with or without resection of the anterior commissure (16 cases). In the remaining 50 cases total laryngectomies were performed.

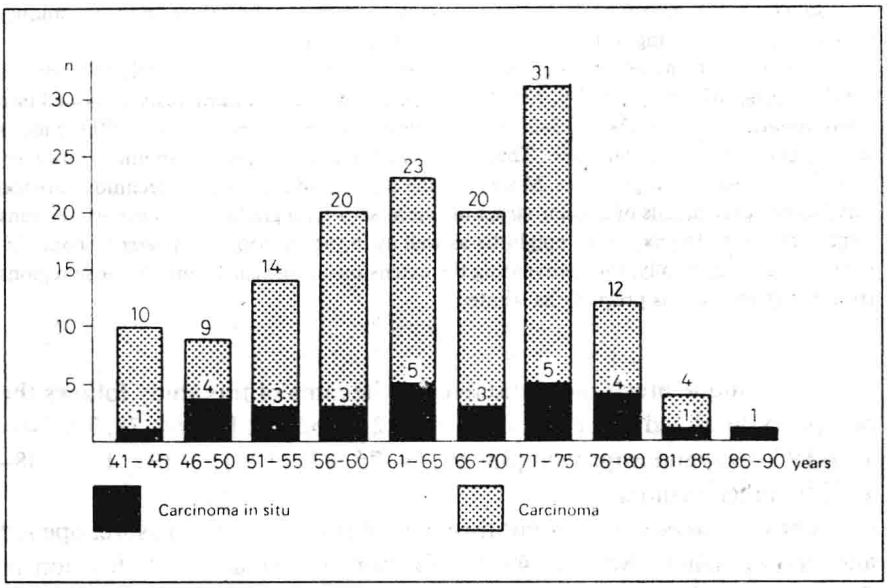

Fig. 1. Age distribution of 144 vocal cord carcinomas.

Primary radical neck dissection was applied in 13 cases, conservative neck dissection in 2 cases, secondary radical neck dissection in 7 cases after the clinical manifestation of metastases in the neck.

Follow-Up. All patients were controlled regularly, the minimum period of follow-up extending over 3 years and the maximum time covering 5 years. (The deadline was March 31st, 1981.) 17 patients died intercurrently, i.e. without evidence of the disease. In all these cases the cause of death could clearly be ascertained. 11 patients died of their laryngeal carcinomas. 46 (57.5%) of the remaining 80 patients were controlled for more than 5 years.

Laboratory Techniques

Surgical *specimens from partial resections* were spread out on a piece of cardboard immediately after excision, drawn and then fixed in formalaldehyde (1:9). The subserial sections were cut strictly perpendicular to the surface in anterior-posterior direction and the slides stained. The technique in these cases was similar to the one described by *Leroux-Robert* [122].

Since *Leroux-Robert* an extensive and detailed amount of literature on the techniques of total organ sectioning of the larynx has been published:

The celloidin embedding was recommended by *Tucker* [212] and modified by others [18–20, 35, 60, 67, 68, 92, 94–99, 126, 127, 196]. The larynx is continuously sectioned into approximately 1,100 slides of 15–20 µm thickness in a coronal plane. Every 50th slide is stained and used for investigation. This time-consuming and expensive method, however, was not suitable for our purposes. Moreover, the sections of the celloidin technique are too thick to perceive details of cellular structures necessary for a grading. In coronary sections large parts of the larynx, in the epiglottis as well as in the anterior and posterior commissure, are cut tangentially, thus preventing the extensions of the carcinoma in those regions from being assessed as precisely as wanted.

A technique much more suitable for the aims of this study follows the principles described by *Leroux-Robert* [122], modified [24, 64, 78, 79, 146–150, 197, 199] and improved [38, 39, 54, 76, 82, 112, 133, 137, 138, 158–162] by other authors.

The *extirpated larynx* is cut through the posterior commissure, opened and photographed. After a 24-hour fixation in formalin (1:4) fixation in formalin (1:9) is continued for 4 further days. With smaller tumours the hyoid bone and the prelaryngeal muscles are cut off, as they are unimportant to our purposes.

The cylindrical laryngeal organ is then cut into eight sectors (fig. 2a–c). The two sectors of the anterior commissure region are close together, whereas those of the posterior commissure are more apart. The sectors are drawn, numbered and decalcified in a 10% formic acid ultrasonic bath protecting the tissue. After dehydration the specimens are double-embedded in paraplast. The sectors are cut into 6- to 8-µm slides and are stained with HE. To mark connective tissues or vessels they are also stained according to the Azan and van Gieson methods. This technique only takes 7–8 days and allows a histopathological examination usually already during the patient's stay in hospital. After the microscopic examination the specimens are magnified 5 times, projected and drawn semischematically (fig. 3).

In addition the intra- and submucous extension of the tumour is illustrated by isomorphic epithelial regions and depicted in a laryngodiagram (LG).

The lymph nodes of the neck (generally 25 of various sizes) are lamellated into two to three sections. The preparation of neck dissection specimens embedded en bloc in celloidin or after 'clearing' with cedar wood oil [60] has proved to be extremely expensive and time-consuming and was therefore considered unsuitable.

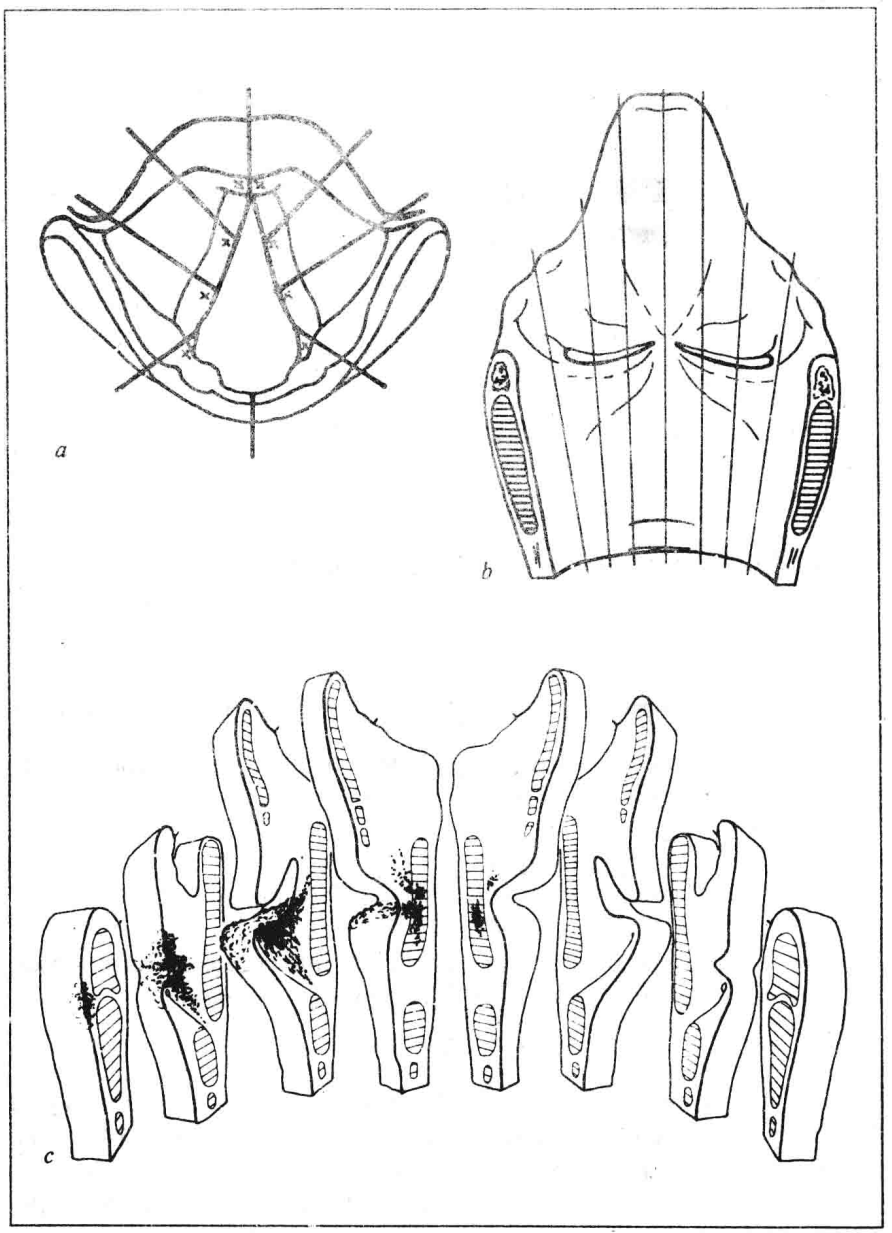

Fig. 2. Location of sagittal sections through the larynx for histological examination. *a* Cranial aspect of diagrammatic laryngeal schema; *b* dorsal aspect; *c* semi-schematic presentation of sectors.

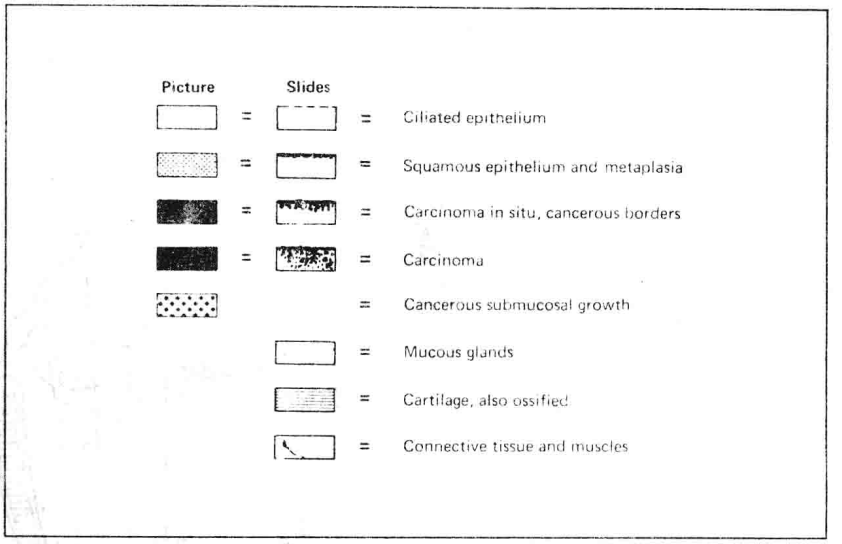

Fig. 3. Explanation of symbols used in laryngodiagrams (LG).

Part of the drawings were produced by *Fleischer* [47] as a part of her promotion thesis.

All histological specimens were prepared by Mrs. *M. Schuler*, first technologist of the Histological Laboratory of the Marburg University ENT Clinic.

Results Concerning Spread and Growth of Vocal Cord Carcinomas

The tumours investigated were subdivided into groups of similar cases, the characteristics of which being assessed in the following:

Carcinomas in situ

The micromorphological structure of the carcinoma in situ has been frequently described before [2, 45, 53, 54, 63, 77, 103–111, 113, 141, 221], therefore here only a short summary is given.

The carcinoma in situ of the vocal cord does rarely differ from the carcinoma in situ of other organs. It is characterized by cellular atypias, enlarged hyperchromatic nuclei and disturbed differentiation, e.g. premature keratinization, multiple and atypical mitoses as well as partial loss of

desmosomes in the epithelial layer. The basal membrane is mostly intact, not 'broken through'. There are no signs of infiltration yet, the malignant lesions are still confined to the epithelial layer.

The differentiation of a carcinoma in situ can vary similar to any carcinoma [43, 53, 103, 104, 109, 110], e.g. basal cell carcinoma in situ, in which the full thickness of the epithelium is replaced by undifferentiated cells, or more differentiated ones, in which only the basal layers show signs of cancerization. Lesions corresponding to a carcinoma in situ may also occur in the adjacent areas of a carcinoma and may be defined as cancerous intra-epithelial extension. They may also occur as isolated foci, separated from the invasive area – so-called concomitant carcinoma in situ [11, 53, 109, 200].

Because of the carcinoma in situ not infiltrating the submucous layer it suffices to present a 2-dimensional extension. The surface spread of the carcinoma in situ in this study is given as a synoptic presentation (fig. 4).

In this synopsis the triangles symbolize the patients, the vertical lines either one or two affected vocal cords. An average vocal cord length of 14–15 mm for males and 10–11 mm for females was assumed. The average vertical height of the vocal cord – 5.5 mm for males and 4.2 mm for females – is pointed out by a thin horizontal line [204, 207]. In the upper half of the figure the anterodorsal extension of the vocal cord lesion is shown, in the lower half the maximum craniocaudal extension, the top part of which showing the parts of the tumour adjacent to the ventricle, the lower part to the subglottic extension.

25 out of 26 carcinomas in situ show a considerably enlarged field of squamous cell epithelium. The ciliated epithelium is obviously changing into a squamous cell metaplasia subglottically, and spreading most extensively in the central and posterior part of the vocal cord and less in the anterior third of it. (This 'apron-like' spread of the pericancerous squamous cell metaplasia can be even better perceived in larger tumours.) A cranial extension of the metaplasia, i.e. towards the ventricle, has not yet been observed in our cases. The hyperplastic squamous cell epithelium mostly shows an acanthosis and parakeratosis. Sometimes scattered basal nuclear atypias can be found (epithelial hyperplasia grade II, epithelial dysplasia medium grade, pericancerous dysplastic epithelial lesions) [54, 104, 105, 108, 109, 188]. Much more rarely the pericancerous epithelium proved to be atrophic. Only in 1 case a small carcinoma in situ could be found in the centre of histologically unchanged epithelium. This patient was a female non-smoker.

In 5 out of 26 cases the carcinoma in situ originated from the centre of the epithelium, most frequently from sites between the anterior and central part of the vocal cord as well as exactly from its rim. In these cases cranially and caudally non-cancerized strips of epithelium could be recognized showing only a simple hyperplasia. These *isolated carcinomas in situ* of 4–5 mm maximum diameter do not yet show definite patterns of extension. All these tumours were characterized by the typical keratotic plaque and clearly differed from their environment.

In most of the cases (21 out of 26) the carcinoma in situ covered parts of the surface of the vocal cord disseminated *like a carpet.* In 9 cases both cords were affected. These cases are characterized by wide extension of the pericancerous squamous metaplasia. The metaplasia was up to 9 mm in vertical height. In 8 cases the carcinoma in situ reached the subglottic boundary between squamous and ciliated epithelium. In the other cases the carcinoma in situ approached this boundary. In these cases a non-invaded strip of squamous cell epithelium is found cranially. So the malignant lesion mostly spreads from 'hotbeds' of cancerization [109]. Their extension usually takes place subglottically, which is especially noticeable in the last 6 cases of bilateral carcinoma in situ which have already exceeded the normal limit of the epithelium by 3–4 mm. In 6 additional cases the whole epithelium of the vocal cord was transformed to a carcinoma in situ. In these cases only, the cancerized epithelium touched the cranial border between ciliated and squamous cell epithelium. *No carcinoma in situ has ever originated out of ciliated epithelium!*

Summary

(1) Nearly all vocal cords affected by carcinoma in situ were covered by enlarged metaplastic and hyperplastic squamous cell epithelium.

(2) The extension of metaplastic squamous cell epithelium mainly occurs in subglottic direction.

(3) Carcinoma in situ originated without exception from the squamous cell epithelium and not from the ciliated epithelium.

(4) A distinction can be made between isolated small tumours without a discernible pattern of spread, which occur less frequently, and disseminatedly spreading carcinomata in situ expanding mainly in the subglottic region, which can be found in most of the cases.

Small Carcinomas of the Vocal Cords (Microinvasive Carcinomas)

The following group consists of cases either defined as microcarcinomas, microinvasive carcinomas or minimal invasive carcinomas described previously [115]. This group is formed by lesions beyond the in situ stage,

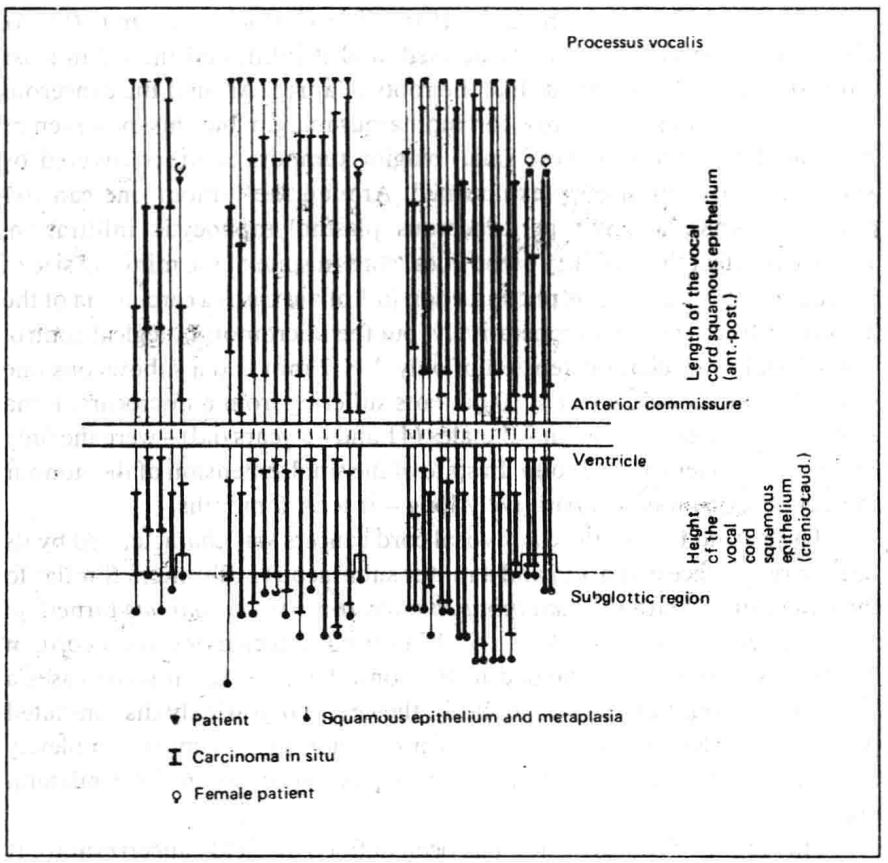

Fig. 4. Synopsis of the extension of the 26 carcinomas in situ of the vocal cords; upper half: length of a vocal cord; lower half: height of a vocal cord (for further explanation, see p. 9).

but not yet invading the muscle of the vocal cord. Here we find – similar to the carcinoma in situ – isolated carcinomas of about 5 × 5 mm surface extension: the actual microcarcinoma. We also find uni- or bilateral widely spreading carcinomas of the vocal cord, the largest parts of which are still in the intraepithelial stage, whereas some others have already started infiltrating in isolated foci or penetrate the submucosa on a wide disseminated front line; so their surface extension does not really allow their classification as microcarcinomas [115].