Minimally invasive endo-laryngo-microsurgery for precancerosis and early cancer of the vocal cords, and a new diagnostic laryngoscopy and surgical training device

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Ph.D. thesis

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Peer-reviewed scientific publications related to the thesis

I. **Paczona R.** (1996)
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V. **Paczona R**, Temam S, Janot F, Marandas P, Luboinski B. (2003)
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INTRODUCTION

The distressing state of health of the Hungarian population is widely known. The death rate due to malignant tumors in Hungary is exceptionally unfavorable. It is the second most common cause of death after heart and circulatory failures, with a rate of approximately 25%. The statistics indicate that the number of patients becoming disabled because of malignant tumors has risen exponentially in recent decades (2).

Laryngeal cancer accounts for 1-2% of all malignancies worldwide, and these are the second most common primary epithelial malignant tumors in the head and neck region. The incidence varies greatly from country to country. According to the most recent data released by the American Cancer Society, approximately 10,000 new cases of laryngeal carcinoma are diagnosed each year in the United States, and 3900 deaths occur there yearly as a result of this disease (4). Spain, Italy and France have the highest rates in the world, but unfortunately Hungary displays too high rates of this disease (1). The European cancer mortality survey placed Hungarian men in first place and women in second and third place as regards the incidence of laryngeal cancer morbidity (2, 3). Laryngeal squamous cell carcinoma will therefore remain a major problem in our country in the near future. Early detection, followed by prompt excision, should be the aim to prevent the development of invasive tumors requiring far more destructive and debilitating surgery.

Endolaryngeal surgery is an integral part of the routine surgical work of an ENT specialist. However, the achievement of adequate surgical training can be a very difficult task because of the variety of new laryngological procedures that have recently been devised. The acquisition of sufficient manual skill in microlaryngoscopy is often problematic. The number of real patients available to current ENT trainees may not be adequate for them to establish competence in all procedures, so there is a need for alternative training platforms.

It is well known, that the development of an invasive vocal cord cancer can be preceded by the chronic persistence of various degrees of premalignant conditions. A marked relationship can be observed between the degree of glottic dysplasia and the risk of further cancerization. The reported incidence of this malignant transformation varies greatly. Patients with keratosis without dysplasia, and those with mild dysplasia, are at low risk of developing cancer (0-5%), whereas those with more severe lesions, such as carcinoma in situ are at a much higher risk (4-30%). Authors agree that special attention must be paid to these patients; appropriate and prompt resection and a careful follow-up are mandatory to prevent further

degeneration. From a surgical standpoint, mucosal stripping of the site of the lesion by cold instrumentation during laryngomicroscopy is commonly considered the treatment of choice. In the past two decades, as in invasive cancer treatment, a new modality of the endoscopic method, CO_2 laser surgery replaced radiotherapy in some centers for the treatment of these cases and especially those involving carcinoma in situ. Successful elimination of precancerous lesions can decrease the incidence of malignant transformation, but its methodology and role have not been analyzed so far.

Both radiotherapy and conservation surgery can effectively treat early-stage invasive glottic carcinoma. Radiotherapy is often recommended instead of surgery because of the better functional voice results as compared with open partial surgery. Nonetheless, radiotherapy has several disadvantages, such as being costly and time consuming, and it may have considerable side effects (edema, mucosal dryness), while partial laryngectomy often requires tracheostomy which has a substantial negative impact on the quality of life in some patients. Besides these conventional oncological approaches, CO_2 laser surgery has emerged as a therapeutic alternative and added a significant dimension to the surgical treatment of laryngeal disorders. However, detailed information and statistical data on local and regional control, final organ preservation rates and survival that might permit a meaningful comparison of laser cordectomy with other treatments for early glottic carcinoma are seldom available in the literature.

Laryngomicroscopy is the gold standard in the diagnosis of glottic precancerosis and early cancers, there is still a need for improvement of our diagnostic armamentarium. Early malignancies of the larynx are usually diagnosed by visual identification, which relies basically on the clinical experience of the examiner in recognizing suspicious lesions during the physical examination. Sometimes, the detection of these early-stage lesions may be difficult during conventional endoscopy with white light, as these lesions sometimes can be indistinguishable from the more common benign inflammatory conditions. For better visualization of these lesions, a new endoscopic method based on photodynamic diagnosis has been developed in the recent years. I had the opportunity to study this new technique in Villejuif (France) and than to introduce it into the practice of our clinic.

AIMS OF THE THESIS

1. To prepare a prototype of a cadaver larynx holder with which to facilitate the acquisition of high-level procedural skills for endolaryngeal surgery techniques during individual or postgraduate teaching courses (Chapter 1).

2. To conduct a retrospective study to evaluate the incidence of premalignant lesions of vocal cords, to find correlation in the malignant transformation into invasive cancer among patients with different degrees of vocal cord precancerosis. To validate the effectiveness and role of laryngomicrosurgery in the elimination of these lesions by analyzing the data on the patients treated in our department during the past 18 years (Chapter 2).

3. To evaluate the long-term (a follow-up of at least 3 years) oncological outcome of a cohort of patients treated by laser cordectomy for early glottic carcinoma in order to assess the statistical data on local control with initial therapy, ultimate local control, regional metastasis rate, organ preservation, overall survival and cause-specific survival. To give evidence for the importance of endolaryngeal CO_2 laser microsurgery, as a first choice of treatment (Chapter 3).

4. To evaluate the feasibility and discuss the diagnostic potential of autofluorescence videoendoscopy as a complementary visual aid in the routine endoscopic diagnosis and in the endolaryngeal surgery of precancerous and cancerous laryngeal lesions (Chapter 4).

1. CADAVER LARYNX HOLDER FOR ENDOLARYNGEAL SURGERY TRAINING

1.1. Introduction and brief history of direct laryngoscopy and endolaryngeal surgery

The history of endolaryngeal surgery dates from the 1850s. The main concept, the most important elements and some of the necessary instruments resulted from the fruitful work of several laryngologists. Many years before the era of indirect laryngeal surgery, *Green* performed the first direct laryngoscopy in 1852; he removed a vocal cord polyp using a modified tongue depressor as a laryngoscope tube (6). Unfortunately, his method was not followed by others, and it was only reintroduced into practice by *Kirstein* in 1895 (11), after several decades of indirect laryngoscopic operations. After the turn of the century direct laryngoscopy gradually gained wider acceptance through the work of *Boyce and Jackson* (2). In 1912, *Kilian* modified the technique, using a suspension apparatus, and thus the operator was able to use both hands for the surgery (10). At the same time, *Brünings* transformed Kilian's suspension laryngoscope and constructed a new device, with which he was able to visualize the glottic area better by compressing the laryngeal framework externally (3). In 1920, *Seiffert* first fixed the laryngoscope tube with a chest holder. By the end of the 1950's, the most important and necessary instruments of direct laryngoscopy had evolved. The next steps in the evolution of direct laryngoscopy, similarly as in otologic surgery, were the application of the operating microscope and the spread of general anesthesia. The first report on laryngomicroscopy was published by *Scalco et al.* in 1960 (21). *Kleinsasser* developed and refined the method and constructed the first set of laryngomicroscopic instruments (12-14).

1.1.1. Surgical training in otorhinolaryngology

The attainment of adequate surgical training is a difficult task in laryngology because of the variety of new procedures that have been devised during recent years. A multitude of innovations in endolaryngeal surgery have also catalyzed new educational initiatives. Manual skills in laryngomicroscopy and phonomicrosurgery are often not easy to achieve in work on patients. Furthermore, phonosurgery requires a sophisticated knowledge of precise anatomical relationships, which can be difficult to express in images. The number of real patients available to current ENT trainees may not be adequate for them to establish competence in all

procedures, and there is therefore a need for alternative *ex vivo* training platforms.

Surgical education has been pursued through a number of techniques to date. These include the use of synthetic practice tools (1, 8 and 19), lifeless cadaveric dissections, lifelike computer-generated practice stations (22, 23), live simulations with animals (5), and the performance of procedures on patients. There is a growing demand on residency and fellowship training programs to measure the levels of surgical competence with regard to general knowledge and also specific skill sets (16, 17). In general surgery and gynecology, a standardized educational testing for trainees has already been introduced into practice (15, 16). Although there are many reports in the literature about temporal bone holders for postgraduate temporal bone surgery (7, 17), a suitable description of a larynx holder platform with which to train in laryngomicrosurgery was virtually unavailable.

In 1994, our clinic organized the first Hungarian endolaryngeal surgery workshop under the leadership of Professor Oscar Kleinsasser, the "doyen" of laryngomicrosurgery. I took an active part in the preparatory work including the designation and preparation of the necessary prototype of a cadaver larynx holder for the "hands on" instructional session. After a careful study of the position of the larynx, patient and suspension laryngoscopic apparatus during laryngomicrosurgery, I designed and constructed a simple platform on my own, which was easily reproduced from readily available materials.

In this chapter I present this cadaver larynx holder (I, III, X), which used to be the only available material for practical demonstration and hands on experience performing different endolaryngeal surgical techniques during postgraduate courses for several years after its construction. Similar devices appeared only in the last two years (4, 18).

1.2. Description of the cadaver larynx holder

The wooden base of the holder and the wooden tilt board (A) are cut out with a circular saw, and joined together by a hinge. They measure 2 cm thick, 12 cm wide and 45 cm long. The angle between them can be adjusted with a special rail (E) from 0 to 45 degrees and fixed by wing-nuts (H) (**Figs. 1.1. and 1.2.**).

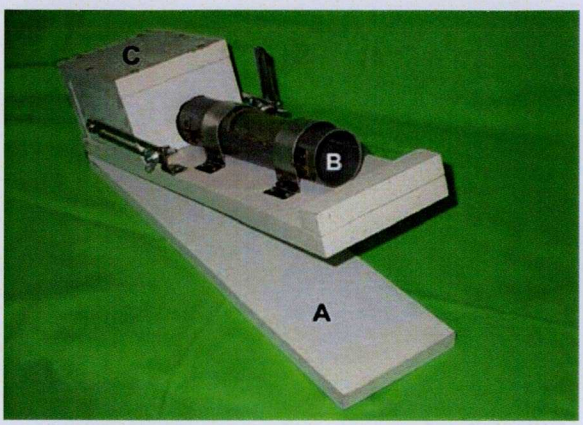


Figure 1.1. Anterolateral view

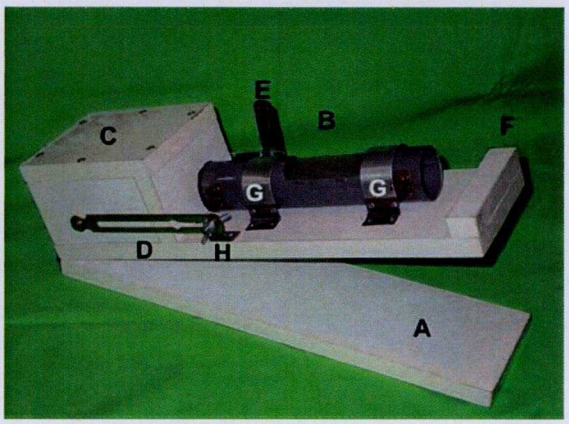


Figure 1.2. Lateral view

A PVC tube (B) with an anterior rubber window is secured to the tilt board by staples. This PVC tube which has a diameter of 5 cm is cut in half and the two halves are attached together by two hinges. The distal end of this tube is closed by a circular plastic sheet to prevent the tissue fluid flowing out from the preparation. A piece 8 cm long and 5 cm wide is cut out from the centre of the upper half (arrow) (**Figs. 1.1. and 1.2.**). This window is covered with a thin rubber sheet, allows practice in for example, translaryngeal operative techniques and better exposure of the anterior commissure by external manual compression of the laryngeal preparation. Two thin steel clamps secure the PVC tube in position (G) and locking nuts and screws secure the tube and tilt board (H).

A wooden box (C) is used to hold the suspension apparatus (dimensions: 12 cm wide, 16 cm long and 13 cm high). Two special rails are situated on its sides and two adjustable metal arms to move the wooden box backward and forward With these its position is adjustable and it may be fixed along the plate with wing nuts (D). This box serves to hold the distal end of the chest holder of the laryngoscope tube and thus imitates the patient's chest.

An additional arm to tilt the apparatus (E) is fixed on the lateral sides of the tilt board. A small wooden board (F) with a thickness of 2 cm, a width of 12 cm and a length of 2.5 cm, to simulate the upper alveolar arch and teeth. The proximal end of the laryngoscope tube leans

against this part of the holder (arrow) (**Figs. 1.3. and 1.4.**).

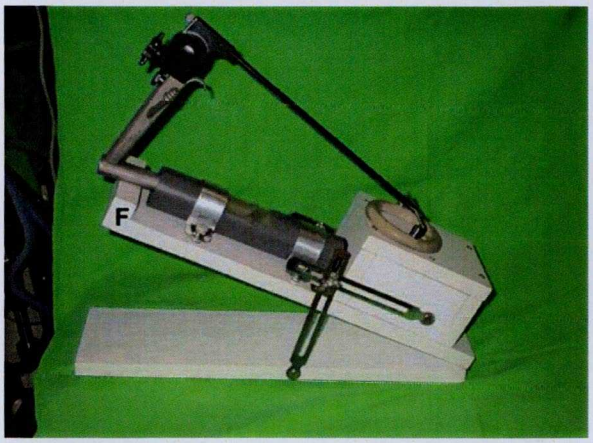


Figure 1.3. Laryngoscope and chest holder in place

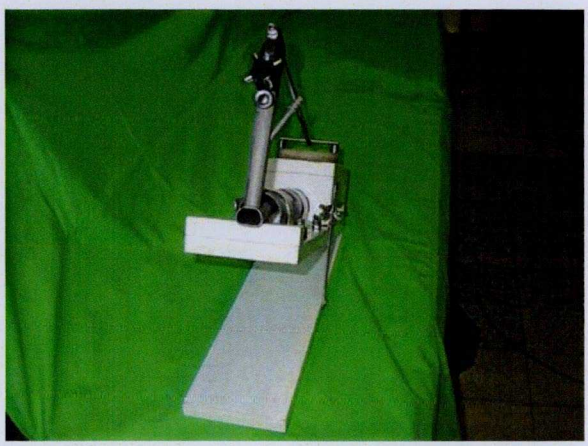


Figure 1.4. Inserted laryngoscope tube

A thin rubber strip on the undersurface of the base ensures a firm grip in order to eliminate slipping.

1.2.1. Preparation of cadaver larynges

Deep-frozen, fresh or formaldehyde solution-preserved cadaver laryngeal preparations can be used in the larynx holder. The deep-frozen cadaver larynx should be taken out of the freezer 6-7 hours before use and allowed to thaw at room temperature. Before the preparation is placed in the holder, it is advisable to cut off the unnecessary tissues, such as the strap muscles, the hyoid bone etc. Before the fresh cadaver larynx is put in place, cotton is placed in the lower portion of the tube to provide a stabilized area and resting place for the trachea. For further stabilization, cotton can also be used to pad the external laryngeal structure (**Fig.1.5.**).

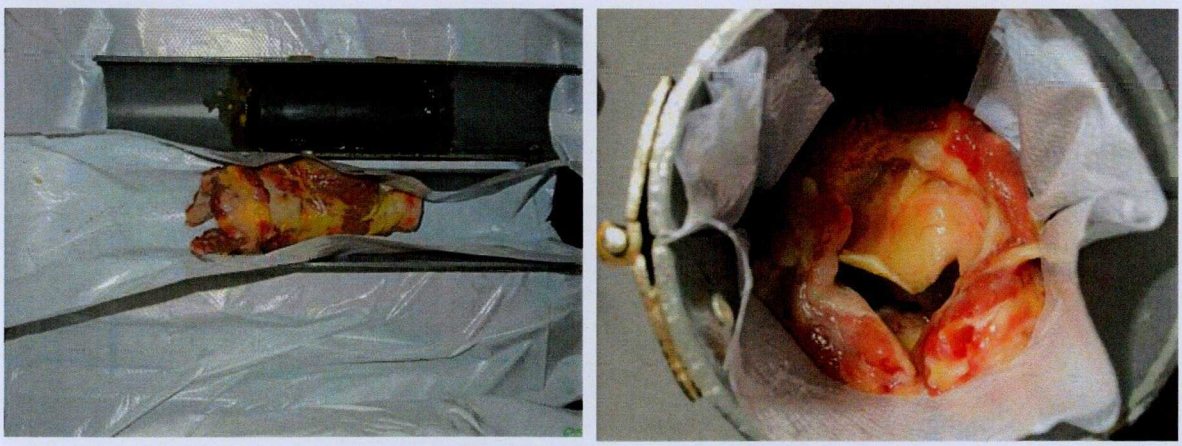


Figure 1.5. Placement of the cadaver larynx

The larynx should be placed onto the lower part of the tube with the epiglottis facing forward at the level of the rubber window, and the upper half should be closed. The tube is secured on the upper basal plate with two specially transformed aluminum hinges and wing-nuts. Next, the laryngoscope tube should be introduced into the larynx from the proximal end of the plastic tube and fixed with the chest holder. The model is then ready; it can be used under an operating microscope with or without a CO_2 laser (**Fig. 1.6.**).

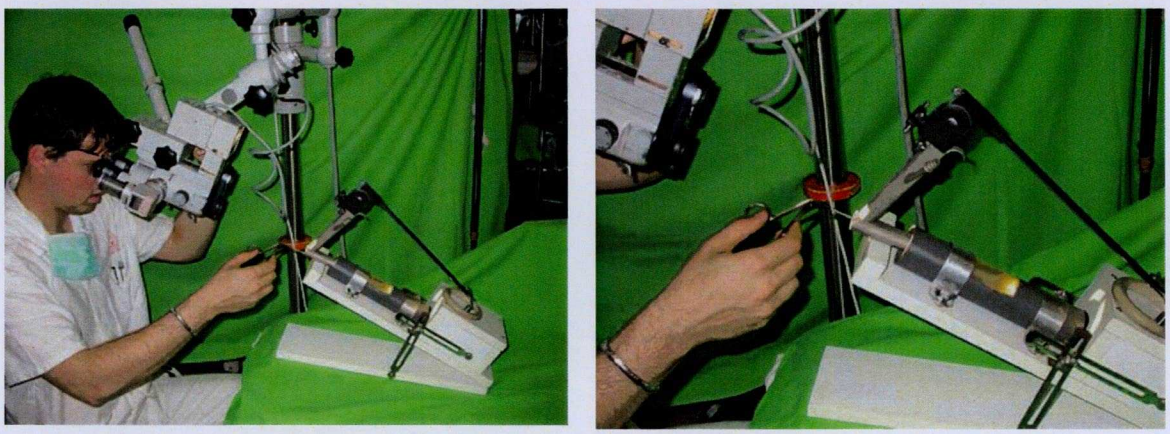


Figure 1.6. The training platform is ready for laryngomicrosurgery training

1.3. Discussion

Use of a temporal-bone laboratory has long been recognized as an essential component in otologic surgical training. The acquisition of adequate surgical training in laryngology is also mandatory because of the variety of new procedures that have emerged in past few years. The most important steps and techniques of old and new methods of endolaryngeal surgery can be learned most safely by practising on cadavers. However, fresh whole-body or whole-head cadavers can be very expensive and require special laboratory space and freezer facilities for storage. The particular advantage of this larynx holder is that there is no need for a special location, such as a dissecting room at the Department of Pathology or Anatomy, as an *ex vivo* harvested cadaver larynx is completely sufficient for the surgical training (I, III, X). This device can be used in existing temporal-bone laboratories, employing cadaveric larynges; accordingly trainees can practise not only otologic, but endolaryngeal surgical procedures.

Solo work is facilitated by the firm fixation of the larynx; the trainee can perform bimanual surgical tasks because there is no need to retract. During endoscopic practice, the plastic tube holding the larynx firmly in place allows maximum variability in position and angle of the introduced laryngoscopes. With this feature, the trainee encounters positioning,

exposure and lighting issues and is rewarded with near-operative conditions for practice. The mastering of laryngomicroscopic techniques is also facilitated by this holder because it permits positioning and exposure identical to those in the surgical theater. The trainee simulates operating room conditions when a microscope, microlaryngeal instruments and his or her choice of laryngoscope are used. The trainee can experience many of the intraoperative conditions necessary to perform laryngomicroscopic surgery, such as the establishment of optimal exposure, lighting and magnification. Further, favorable ergonomic habits such as comfortable body positioning are acquired and familiarity with the instrumentation and technical nuances should accelerate intraoperative learning.

Varied techniques for the resection of benign and malignant tumors of the glottis can be practised and anatomic fundamentals reinforced. Examination of the vocal cord structure with high-power magnification is critical for endolaryngeal surgical competence. The application of a subepithelial injection of saline can be practised and helps the surgeon to master techniques to attain maximal preservation of the superficial lamina propria, often critical for an optimal postoperative voice.

The rubber window located anteriorly on the PVC tube allows endo-extralaryngeal placement sutures for both reversible and irreversible vocal cord and arytenoid lateralization. The placement of keels and stents through the rubber window (which would correspond to the skin) can also be simulated. Additionally, CO_2 laser resection techniques can be learned and practised.

This prototype laryngeal holding device is intended for use with cadaver human or mammalian (porcine or sheep) larynges. It designed to minimize cost, and to maximize utility, adaptability and versatility. It is constructed from inexpensive, easy-to-find wood, plastic and metal components that furnish a firm support (I, III, X). The original idea of this simple model was connected with the organizational preparations of the first Hungarian laryngomicroscopic workshop held in Szeged in 1994. *For a long time it was the only available material in international literature for practical demonstration and hands on experience* and for performing different endolaryngeal surgical techniques during postgraduate courses. Similar devices appeared only in the last couples of years (4, 18). Since its first construction, it has proved to be a unique and a very useful tool that was tested and utilized in a local institution and in many advanced international endolaryngeal surgery courses.

2. OVERVIEW AND RETROSPECTIVE ANALYSIS OF GLOTTIC PRECANCEROSIS

2.1. Introduction and classification of glottic precancerosis

It is well known that more than 90% of the malignant tumors of the larynx are squamous cell carcinomas and believed to often develop from precancerous epithelial lesions (21). Both the classification of dysplastic lesions of the larynx and the most appropriate treatment have been topics of debate since 1930, when the concept of laryngeal keratosis or pachydermia laryngis as a premalignant disease and the concept of preinvasive cancer emerged. In the 1960s, the histological changes were suggested as the basis for the classification of hyperplasias of the laryngeal squamous epithelium as three stages of precancerosis instead of the various synonyms derived from the surface appearance of the epithelium of the vocal cords (5, 16, 17, 20, 23). Since laryngeal carcinoma develops from stratified squamous epithelium, it is obvious that there are parallels between carcinogenesis of the laryngeal mucosa and carcinogenesis in other organs with squamous epithelial lining. Precancerous lesions of mucosa lined with squamous epithelium have been intensively studied in the region of the portio vaginalis uteri and the oral cavity. Investigations have focused on their macroscopic clinical appearance, as well as histological changes (2). The application of results gained by these studies also helped to better understand the laryngeal precancerosis.

Clinically precancerous lesions are white and red patches (pachydermia), referred to as leukoplakia and erythroplakia, respectively. However, it has now been acknowledged that the diagnosis of a precancerous lesion of the larynx and the evaluation of its potential to progress must be based on the histological characteristics of the lesion itself; the histological nature of leukoplakia is completely unpredictable prior to biopsy (10), due to the fact that identical macroscopic appearances can correspond to different histological patterns. The term keratosis denotes a hyperplastic laryngeal lesion involving an increase in the epithelial layers of the larynx. This can be distinguished as keratosis without dysplasia, or simple hyperplasia, when the hyperplasia involves the layer of the basal cells of the stratified epithelium or undifferentiated reserve cells of the columnar epithelium, or as keratosis with dysplasia, when the maturation of the cell elements is altered. In mild dysplasia, cell stratification is easily identified, whereas in the severe form, the altered cell maturation leads

to the subversion of cell polarity, with severe alterations in stratification. The histological classifications of precancerous laryngeal lesions, most closely followed in the literature for clinical purposes, are based on evaluation of the grade of hyperplasia and/or dysplasia of the epithelium (34). *Hellquist et al.* (11, 12) distinguish between Grade 1 lesions, presenting hyperplasia and/or keratosis with or without mild dysplasia, Grade 2, characterized by moderate dysplasia, and Grade 3, in which the dysplasia is severe or of such a type as to configure carcinoma in situ. This classification is based on one proposed by *Kleinsasser* in 1963 (20) and by *Duchon and Czigner* (5), *Sugár et al.* (33, 34) in Hungary, who distinguished a first class characterized by simple squamous cell hyperplasia, a second class represented by squamous cell hyperplasia with atypia, and a third class represented by carcinoma in situ. *Friedmann* in 1974 proposed (8) that dysplastic lesions of the larynx be considered on the same scale as the corresponding lesions of the uterine cervix, which are viewed as different development phases of a single picture of intraepithelial neoplasia. Thus, this classification distinguishes keratosis without dysplasia from keratosis with mild dysplasia (laryngeal intraepithelial neoplasia, or LIN 1), moderate dysplasia (LIN 2), and severe dysplasia or carcinoma in situ (LIN 3).

The data emerging from the various studies confirmed that dysplastic lesions of the larynx can potentially develop into malignant epithelial lesions (1, 3, 5, 30). This capacity to develop is correlated with the grade of dysplasia of the epithelium, since the percentage of malignant transformation increases in proportion to the increase in severity of dysplasia (13, 15). In an earlier publication based on our 10-year experience we reported a lower rate of malignant transformation than other authors (II). We found, that the number of glottic precancerosis turned into malignant transformation is much lower than the incidence of glottic cancer, and the pathway from keratosis with atypia to invasive carcinoma might be observed more rarely than the glottic cancer itself. Thus, we concluded that most of the laryngeal cancers cannot be assessed as the progression of precancerous lesion (II).

The treatment policy for dysplasia and carcinoma in situ of the glottis varies considerably from one hospital to another, some physicians favoring local excision such as stripping or CO_2 laser excision of the vocal cords, others preferring open cordectomy or a full dose of radiotherapy (29, 32, 35, 38).

In this chapter, I would like to present the results of our retrospective study to evaluate the incidence of premalignant lesions of the vocal cords, to find correlation with the

malignant transformation into invasive cancer among patients with different degrees of vocal precancerosis, to validate the effectiveness and role of laryngomicrosurgery in the elimination of these lesions by analyzing the data on the patients in our department during the past 18 years.

2.2. Patients and Methods

This study is based on the review of a series of 2827 patients who underwent therapeutic laryngomicroscopy at our department between January 1987 and March 2004. 183 patients of them (161 males and 22 females) presented with various degrees of keratosis of the laryngeal epithelium, with or without dysplasia. The patients were subdivided by using the following classification, based on the presence and grade of any dysplasia observed. Of the 183 patients, 97 (53.0%) presented with keratosis without dysplasia, 45 (24.6%) with keratosis with mild dysplasia, 13 (7.1%) with keratosis with moderate dysplasia, 16 (8.7%) with severe dysplasia, and 12 (6.6%) with carcinoma in situ (**Table 2.1.**).

Grade		*Number of patients*
Group I	Simple keratosis without atypia	**97** (53.0%)
Group II	1: Keratosis with mild dysplasia	**45** (24.6%)
	2: Keratosis with moderate dysplasia	**13** (7.1%)
	3: Keratosis with severe dysplasia	**16** (8.7%)
Group III	Carcinoma in situ	**12** (6.6%)
Total		183

Table 2.1. Grading of glottic precancerosis

All patients were submitted to excisional biopsy with direct suspension laryngomicroscopy, all lesions were removed completely and the specimens were sent to histological analysis. Depending on the exact pathological grading, the following further treatments were decided. In case of keratosis without dysplasia only wait-and-watch policy was initiated; patients presenting with lesions with severe dysplasia or carcinoma in situ were treated additionally with endolaryngeal microscopic surgery ("cold technique") or surgery via a CO_2 laser, depending on the site and extent of the lesion.

Patients presenting with keratosis without dysplasia and those with mild or moderate

dysplasia were followed up approximately every 3 months for the first year and thereafter every 6 months. Patients with severe lesions or carcinoma in situ were checked approximately every 2 months for the first year and every 3-4 months thereafter. Patients were followed up for a mean period of 68 months (range 7-126 months).

2.3. Results

The highest incidence of vocal cord hyperplasia was found in the 5th, 6th and 7th decades. The youngest patient was 21 and the oldest 89 years of age. The mean age was 56.7 years. Of the 183 patients, 161 were males ranging in age from 21 to 89 years, and 22 were females ranging in age from 35 to 73 years. The sex ratio of males and females was 5:1. For groups I, II and III, the mean ages were 48.9, 55.1 and 59.3 years, respectively.

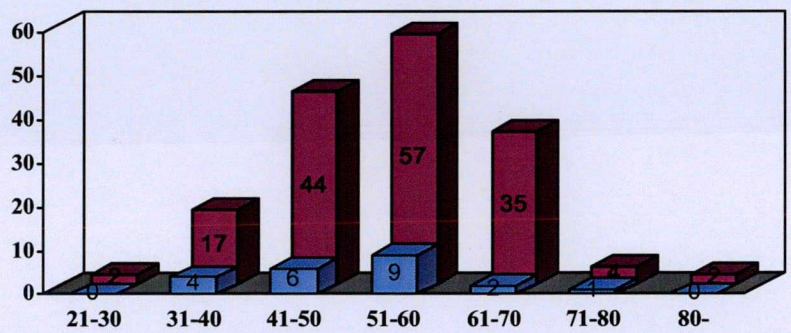


Figure 2.1. Age and sex distribution of patients with glottic precancerosis

The main presenting symptom in almost 100% of the patients was hoarseness, although some other complaints were observed to associate with dysphonia, e.g. dyspnea (13%) and hemoptysis (4%). The average duration of the symptoms was 7 months.

Only 35 patients (19%) were nonsmokers; the remaining 148 patients (81%) were all cigarette smokers. 28 patients (19%) smoked fewer than 10 cigarettes/day; 38 patients (26%) 10-20 cigarettes/day; and 82 patients (55%) more than 20 cigarettes/day (**Fig. 2.2.**).

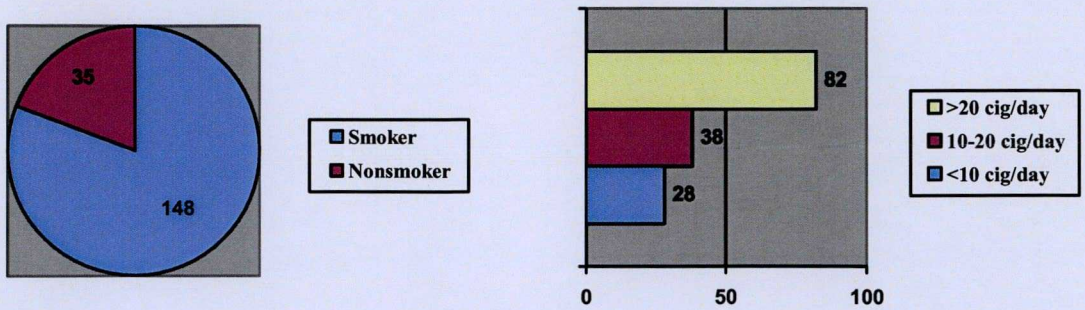


Figure 2.2. Smoking habits and daily tobacco consumption

The duration of tobacco abuse varied as follows: 9 patients had smoked for less than 10 years; 21 patients for 10-20 years; and 118 for more than 20 years. 81 of the 183 patients (44%) were abstinent, whereas the remaining 102 (56%) consumed alcohol regularly (**Fig. 2.3.**).

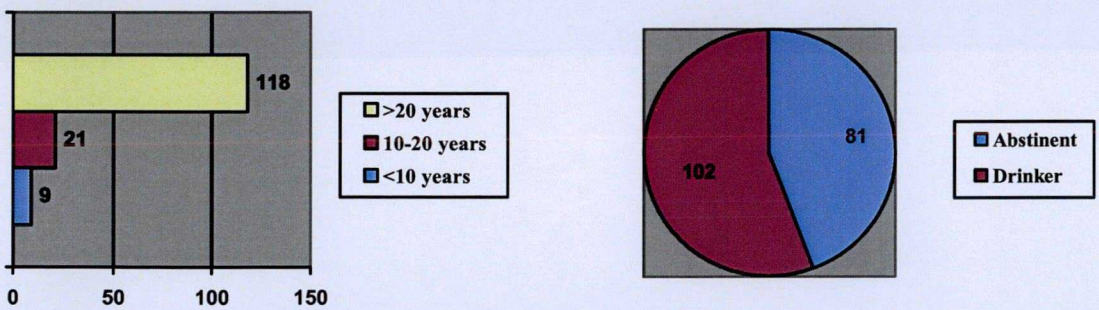


Figure 2.3. Duration of smoking, drinking habits

The lesions were localized equally both vocal cords. The anterior two-thirds of the cords was the most frequently affected (n = 122); the whole length of one or both vocal cords was involved in 61 cases.

Of the 183 patients with dysplastic lesions of the larynx 165 (90.2%) cases were resolved by the first treatment, but 18 (9.8%) had recurrences. Of these 18 patients, 12 had a single recurrence and 6 multiple recurrences.

2.3.1. Canceration into invasive carcinoma

Hyperplasia or keratosis without dysplasia

As concerns the evolution of the lesions, none of the 97 patients presenting with keratosis without dysplasia, exhibited further malignant progression of the disease. In 1 case a second primary tumor has been observed in the left bronchial tree and treated by chemotherapy 8 years after the first excisional biopsy of the vocal cord lesion.

Keratosis with mild dysplasia

Of the 45 patients with keratosis with mild dysplasia, 2 cases developed directly into invasive squamous cell carcinoma. One of these 2 patients did not attend the follow-up examinations regularly and he returned to our clinic only when a T2 N0 stage tumor occurred on the right vocal cord 6 years after the keratosis was diagnosed. CO_2 laser cordectomy was performed, and he is doing well. The other case developed directly into invasive carcinoma 4 years after the first biopsy was taken. Total laryngectomy was performed, but 1 year later the patient died due to a locoregional recurrence. Another patient in this group developed a very rare soft tissue tumor (a laryngeal leiomyosarcoma) 1.5 years after the first intervention. He underwent total laryngectomy and functional neck dissection on the left side.

Keratosis with moderate dysplasia

As regarding the 13 patients with lesions classified as keratosis with moderate dysplasia, 1 patient underwent further progression: subsequent development into cancer occurred 2 years after the initial diagnosis. Subepithelial superficial CO_2 laser cordectomy was performed, and the patient is now doing well without any signs of recurrent disease.

Keratosis with severe dysplasia

Of the 16 subjects with severe dysplastic lesions, 1 patient suffered a recurrence of the lower grade (moderate dysplasia) on the opposite vocal cord 1 year later, which then developed into invasive carcinoma 3 years after the initial diagnosis. The histology confirmed the presence of an invasive carcinoma, and total laryngectomy was performed. Another, relatively young patient (37 years old) displayed malignant transformation 13 months after the first biopsy. He underwent total laryngectomy, and 1 year after the surgery is doing well without any signs of recurrent disease.

Carcinoma in situ

12 patients with carcinoma in situ were observed. 7 of them underwent wide endolaryngeal excision of the glottic lesions by a conventional surgical method (stripping with cold instruments) and followed up by a wait-and-watch policy. 5 patients participated in different additional surgical procedures: 4 of them were treated by CO_2 laser cordectomy while endolaryngeal cordectomy without laser was performed in 1 patient. One of them received full-dose radiotherapy because the second histological examination revealed the signs of microinvasion. None of them developed recurrences or invasive carcinoma after surgery.

Development into cancer occurred with direct progression in 6 cases (3.3%). The latency period between the initial diagnosis and the development of cancer ranged between 13 months to 6 years (mean 35 months). On the occasion of a second biopsy within 3 months to 1 year 7 other patients were found to have invasive cancer and were excluded on the assumption that the first biopsy had been unrepresentative by missing the cancer.

2.4. Discussion

Smoking and the consumption of alcohol are known risk factors for laryngeal cancer (5, 9, 26, 36), and this is also in agreement with our case histories. A failure to alter the lifestyle (regularly observed in those patients who presented with progression of the initial lesion) may well be one of the real factors responsible for the progression of the disease.

Dysplastic lesions of the larynx have the potential to develop into frankly malignant lesions. This capacity to develop significantly correlates with the grade of dysplasia of the covering epithelium, since the percentage of malignant transformation increases in proportion to the increase in severity of the dysplasia (17, 19, 24). Many studies have noted that the incidence of malignant degeneration in patients with keratosis without atypia is very low, not more than 3-4%, in sharp contrast with the patients who have atypia. In the latter group of patients, the literature data indicate an incidence between 16 and 40% (13, 15, 28). Comparison of our data with those reported by others reveals a close correspondence of the rates of transformation into invasive carcinoma, above all in those patients with mild and moderate dysplasias (**Table 2.2.**).

Author, year	Keratosis without dysplasia	Keratosis + mild dysplasia	Keratosis + moderate dysplasia	Keratosis + severe dysplasia and cc. in situ	Total
Velasco, 1987	1/46 (2.2%)	NA	6/31 (19.3%)	2/10 (20%)	9/86 (10.3%)
Sllamniku, 1989	**18/604 (4.1%)**	**15/204 (7.3%)**	**4/23 (17.3%)**	**25/90 (27.7%)**	**62/921 (6.7%)**
Blackwell, 1995	0/6	3/26 (11.5%)	5/15 (33.3%)	5/18 (27.8)	15/65 (20%)
Gallo, 2001	**6/143 (4.1%)**	**4/56 (7.1%)**	**6/28 (21.4%)**	**3/32 (9.3%)**	**12/259 (7.3%)**
Motta, 2001	NA	5/89 (5.6%)	1/14 (7.1%)	5/38 (13.1%)	11/141 (7.8%)
Our study	**0/97**	**3/45 (6.7%)**	**1/13 (7.7%)**	**2/28 (7.1%)**	**6/183 (3.3%)**

Table 2.2. Incidence of transformation of dysplastic laryngeal lesions into carcinoma, according to various authors (NA= not available)

Nevertheless, it emerged from our study, are at only in agreement with other authors (10), that patients with keratosis without dysplasia present a low risk of developing cancer, whereas those with more severe dysplasias or with carcinoma in situ are at a much higher risk. Consequently, in the latter patients, it seems appropriate to consider more aggressive treatment (10, 31, 38). The treatment of carcinoma in situ probably means the most difficult decision (7, 11, 16). This uncertainty is reflected in the variations of the different treatment modalities (27, 28, 29, 38). A number of reports suggest that the incidence of invasive cancerization derived from carcinoma in situ is rather high, 21-30%, despite all kinds of treatment (27). Some author favors radiation therapy, while others (in agreement with our opinion) have pointed out that there is a place for a more conservative treatment policy, e.g. the surgical excision and the close follow-up of the patients (16, 20, 29, 32, 35).

It must be recommended that patients with dysplasia in the laryngeal epithelium be observed regularly, with special attention to the groups in whom more pronounced atypia has been demonstrated. Another important factor is the duration of the follow-up, which must be appropriate in length, with regard to the fact that the tendency to transformation may occur even several years after the initial diagnosis (4, 10, 17).

However, it is likely that there are other factors besides those already known that can influence the progression of the disease. This would explain why lesions of the same grade develop into carcinoma only in certain patients and why lesions of lower grades can develop into malignancies without going through any of the intermediate stages.

If we compare the rate of malignant transformation of glottic precancerosis and the incidence of glottic cancer, it is obvious that the pathway from keratosis with atypia (6 cases from 183) to invasive carcinoma is observed more rarely than the occurrence of glottic

cancer itself. Further studies on the subcellular changes and oncogenes of tissues involving dysplastic lesions will certainly lead to more details on these aspects, indicating whether they will evolve or not (22, 24).

Experience during the past 30 years has been sufficient for laryngologists to recognize and understand the nature of glottic precancerosis. In the 1960s, all whitish lesions of the vocal cords were excised on the supposition of their possible transformation into invasive cancer. Our treatment policy became more conservative: bilateral, symmetric whitish lesions of the vocal cords are removed only in case of progression or chronic persistence and, with the improvement of the laryngomicrosurgical technique the indications for the excision of these lesions became more precise (14, 31). Our last 8 years' observations and experience support our previous conclusions and results which were reported on in earlier publications (II, VII). The number of the treated precancerosis, mainly those, which transformed to invasive cancer from them, is much lower than the number of vocal cord cancers without any pathway of precancerosis. This difference represents a significant disproportion, which is inconsistent with the theory that premalignant lesions always precede invasive cancer of the vocal cords. In our opinion, carcinogenesis presumably has different forms in regard of its duration and aggressiveness. Dysplastic lesions of the vocal cords have the dangerous potential to develop into invasive malignant lesions. Our method to eliminate these lesions during laryngomicroscopy with or without CO_2 laser proved to be efficient. This is demonstrated by our results: the percentage of the malignant transformation is minimal, and in cases of in situ carcinoma, none of our patients showed degeneration into invasive squamous cell form (II, VII).

3. MINIMALLY INVASIVE CO_2 LASER SURGERY FOR PRECANCEROUS LESIONS AND EARLY CANCER OF THE VOCAL CORDS

3.1. Introduction and background of endoscopic-microscopic CO_2 laser surgery

Carcinoma of the glottis is usually diagnosed in the early phase of the disease; spreading to regional lymph nodes is seldom seen, and distant metastases are extremely rare. These pathological characteristics and the fact that effective treatment is available are the basis of the relatively good prognosis of this malignancy (40). The goals of treatment include cure, laryngeal voice preservation with optimal voice quality, minimal morbidity, expense and inconvenience. The selection of treatment depends on the location and extent of the tumor, the medical condition of the patient, the philosophy of the physician, the tradition of the hospital or clinic and the wishes of the patient. These tumors may be treated with cordectomy by thyrotomy, radiotherapy or transoral laser excision. In many countries, radiotherapy is still the first choice of treatment, offering a low rate of recurrences, and good tumor-specific and overall survival, and the quality of the voice is also reported to be good. However, some authors advocate that radiotherapy is too time-consuming, expensive, and can be considered "overtreatment" in this group of patients (11, 12, 44, 45).

The surgical approach of using CO_2 laser for endolaryngeal operations was introduced by *Jako and Strong* in 1972 (24, 46). It was subsequently utilized for the treatment of benign laryngeal lesions, e.g. papillomas and congenital and acquired upper airway stenoses (2, 26). For the treatment of malignancies, lasers were introduced more slowly and were restricted to only a few centers throughout the world. The first reports of successful cures with lasers in cancer surgery were published in 1975 by *Strong* (46). Initially, the application of laser was limited to the excision of early vocal cord tumors, and the guidelines regarding the indications and technical details of laser tumor surgery then gradually evolved (7, 49).

In Europe *Burian and Höfler* were the first to treat glottic carcinoma effectively with laser (6). Since then, a number of studies have been reported on the oncological outcome of patients treated with lasers by *Steiner* (44, 45) from Göttingen, *Werner and Rudert* (39) from Kiel, *Eckel and Thumfart* (15, 16) from Cologne, *Motta* (30) from Naples and *Remacle* (36) from Brussels and the basic concept of minimally invasive laser surgery has gradually been clarified and become well established. The principle of minimally invasive surgery is to minimize surgical morbidity while adhering to long-standing oncologic standards, performing

a complete resection of the tumor while preserving as much function as possible.

This new method was rapidly introduced into the clinical routine in Hungary, too. *Bánhidy and Kásler* (3) published the first paper on the indications and the technique, while *Németh and Bánhidy* (33) reported on the combination of laser and postoperative radiotherapy. *Élő et al.* (17) applied laser resection in cases of local recurrence after radiotherapy. Since 1987, our team, led by *Prof. Jenő Czigner* has published several papers on good oncological and functional results, clearly demonstrating the clinical applicability and usefulness of this method (9-13). After become familiar with the laser dissection technique, our team proposed a new classification and subgroups of endoscopic cordectomies. In 2000, partially on the basis of these results and publications (11, 12) the Nomenclature Committee of the European Laryngological Society officially created a new classification for laser cordectomy (37).

Although laser surgery has achieved a key position in minimally invasive concepts in the treatment of benign tumors or stenosis of the upper aerodigestive tract, the controversy is ongoing as to whether laser excision or other treatments should be offered for early glottic carcinoma. To answer this question correctly, specific information is needed regarding the oncological outcome of each method. However, detailed literature information on local and regional control, final organ preservation rates and survival that might permit a meaningful evaluation of laser cordectomy is extremely rare (15, 16).

In this chapter, I would like to report on our prospective study of the long-term oncological results of endoscopic laser surgery for Tis, T1 and T2 glottic carcinoma, presenting the treatment modalities and results and comparing these results with other conventional methods for early glottic cancer treatment.

3.2. Patients and methods

Between May 1987 and March 2004, 259 patients with early-stage glottic cancer were endoscopically treated by CO_2 laser at the Department of Otolaryngology of the University of Szeged. 167 of them satisfied the criterion of having a follow-up at least 36 months, so the statistical analyses were performed on this group.

The tumors, classified according to the 2002 UICC (Union Internationale Contre le Cancer) TNM system, included 8 Tis, 153 T1 (128 T1a and 25 T1b), and 6 T2 lesions. The

patient population included 156 men and 11 women with a mean age of 60.01 years (range, 35 to 82 years) (**Figs. 3.1.**).

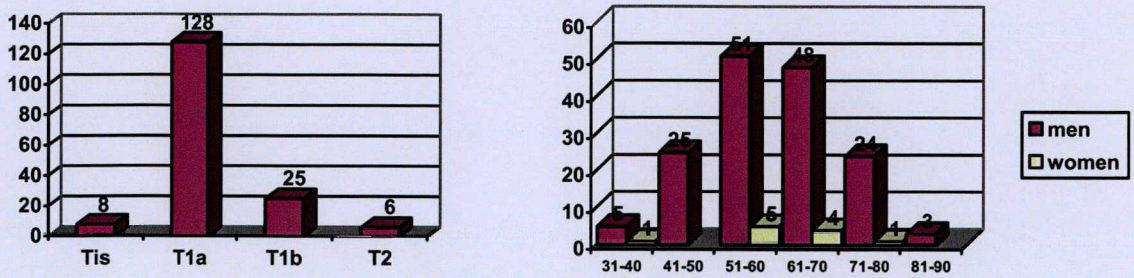


Figure 3.1. TNM staging of the vocal cord tumors and distribution of patients by age and gender

The distribution of the histopathological results on the operative specimen is depicted in **Fig. 3.3**. Histological examination revealed that of the 148 epidermoid carcinoma samples 116 involved well-differentiated, 31 moderately-differentiated and only 3 poorly-differentiated epidermoid tumors. In 10 cases carcinoma in situ, in 7 cases the verrucous form, and in 1 case lymphoepithelioma-like carcinoma and in 1 case leiomyosarcoma were diagnosed.

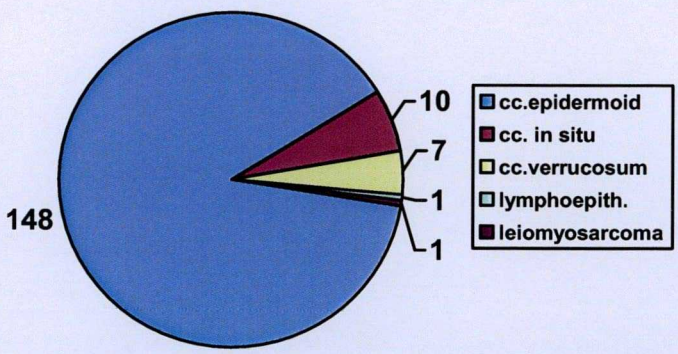


Figure 3.3. Histology of resected glottic tumors

With the exception of 73 patients who had undergone random biopsy or mucosal stripping for diagnostic purposes elsewhere and were therefore enrolled at our institution for subsequent endoscopic treatment, none of the other patients had been previously treated.

The tumor extensions and the histology of the surgical margins are depicted in the **Fig. 3.4.**

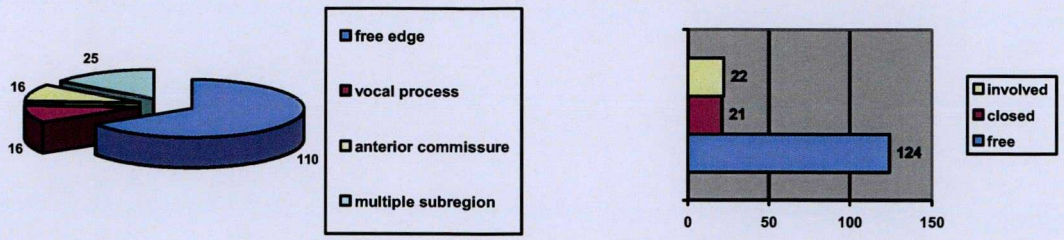


Fig 3.4. Tumor extension and histology of the resected specimens

All patients underwent staging endoscopy of the oral cavity, larynx and pharynx to allow a detailed assessment of the tumor present and to rule out other synchronous neoplasms. Patients with clinically negative necks were not offered additional prophylactic treatment for the cervical lymph nodes. The mean duration of hospital stay was 4.1 days.

All patients were followed up with periodic videoendoscopic examinations, scheduled every 2 months in the first 2 years and with decreasing frequency thereafter. All patients in the present series had at least 3 years of follow-up (last consultation on March 2005). The mean follow-up was 82 months (range, 36 to 177 months).

Recurrence was defined as a biopsy-proven neoplastic lesion treated less than 60 months earlier. For longer time intervals, we defined the lesion as a second laryngeal tumor, regardless of its site of origin.

3.2.1. Implications of preoperative assessment and indication

Early-stage glottic cancer encompasses a variety of lesions ranging from superficial neoplasia involving a portion of the vocal cord to tumors infiltrating the vocal muscle or extending to the paraglottic space. In order to evaluate these lesions correctly and to choose the best resection type, careful pre- and intraoperative assessment were carried out in every case. Radiologic evaluation by computed tomography scan or magnetic resonance imaging was not been applied routinely in our cases.

Our preoperative diagnostic work-up included a thorough physical examination, and office laryngoscopy with flexible or rigid telescopes with angles of 70 ° or 90°. Video-laryngostroboscopy allowed multiple perspectives of the lesion and analysis of the vocal fold movements. Macroscopic characteristics, color, the superficial spreading of the lesions and vocal cord mobility were also inspected. Intraoperatively, the laser resection was also

preceded by microlaryngoscopy and palpation with instruments of the vocal cords. Autofluorescence endoscopy has recently proved to be a reliable complementary technique in the evaluation of these lesions (see Chapter 4).

3.2.2. Surgical techniques

Tumor resection under microlaryngoscopy was performed from 1987 to 2000 with a Tungsram TLS 61 surgical CO_2 laser (Tungsram, Hungary), and subsequently with an Opal-25 surgical CO_2 laser (Lasram Ltd., Hungary), coupled with a micromanipulator and a Zeiss operating microscope. The laser was generally set at an output power of 5–15 W in a continuous mode at a spot size of approximately 0.8 mm^2. All patients were intubated transorally for surgery. All patients received 40-125 mg of methylprednisolone intravenously during the intervention and 40-80 mg of the same drug during the first few days after surgery, if necessary. Extubation was performed 5–10 min after the end of the intervention, and patients were observed closely for airway control after extubation. Different sizes of laryngoscopes (Storz Company) were used to expose the larynx.

3.2.2.1. Surgical resection without preoperative histology

The surgical technique without preoperative histology consisted in systematic exposure of the lesion with a laryngoscope tube; for better visualization of the affected area the homolateral false vocal cord was also resected in some cases. The dissection with the laser beam was performed on healthy tissue, leaving a resection margin of at least 2-3 mm around the neoplasia, and one-piece, "en bloc", removal of the tumor was used.

3.2.2.2. Surgical resection with preoperative histology

Previous biopsy or mucosal stripping might alter the endoscopic appearance of the lesions significantly, so that planning of the appropriate resection line can be complicated. In such cases, our resection was always wider and more extensive and more healthy surrounding tissue around the tumorous lesions was sacrificed in order to ensure oncologically safe surgical margins.

No routine frozen sections were obtained in the operating room after laser resection. Specimens were resected in one piece, oriented anatomically after removal on a cork plate

and fixed in 4% formaldehyde solution to facilitate histopathological examination of the margins.

3.2.3. Statistical analysis

The 5-year actuarial survival was determined without correction for age or intercurrent death from the date of the primary operation until the date of the last follow-up examination or death. Local control with initial treatment, ultimate local control, regional control, larynx preservation rates and overall survival after 5 years were likewise calculated. For tumor-specific actuarial survival (tumor-related survival), patients dying disease-free of unrelated causes were censored at the time of their death. Follow-up for this study was continued until 31 March 2005. The follow-up duration ranged from 36 to 177 months (median 82 months).

Survival rates were computed by using the product-limit estimator of Kaplan-Meier. Data were analyzed with the statistical package for the social sciences (SPSS) for Windows statistical software package version 9.0.

3.2.4. Acoustic voice analysis

Voice studies were recorded at least 6 months following surgery. For the registration of acoustic signals, we used a Pentium III 1.6 GHz computer with 256 Mb memory and Sound Blaster Live sound card. For the acoustic voice analysis Praat software (4.1.12) for Windows XP was used. A high-resolution microphone was placed 10 cm from the mouth whilst vowels were pronounced at a comfortable frequency and tones in a sound-proof chamber. For the aerodynamic evaluation, we used the maximum phonation time (MPT) for the Hungarian vowel (í). Once the signal is processed, the computer calculates the following acoustic parameters: the fundamental frequency (F0), the Jitter or frequency perturbation (%), the Shimmer or amplitude perturbation (%) and the NHR (noise harmonics ratio) which measure the degree of noise produced when air escapes through the glottis whilst emitting a vowel.

3.3. Results

Among the 167 patients treated with endoscopic laser surgery, none had lymph-node or distant metastases on initial presentation. Accordingly, all these patients were treated with microlaryngoscopic surgery alone.

3.3.1. Subgroups of laser cordectomies

After become familiar with the laser dissection technique, our team proposed and subsequently used the following subgroups of endoscopic cordectomies. Lesions limited to the surface of the true vocal cords, i.e. small carcinoma in situ or exophytic superficial tumors, were dissected submucosally, above the muscular layer by "superficial" cordectomy (**Fig.3.5**).

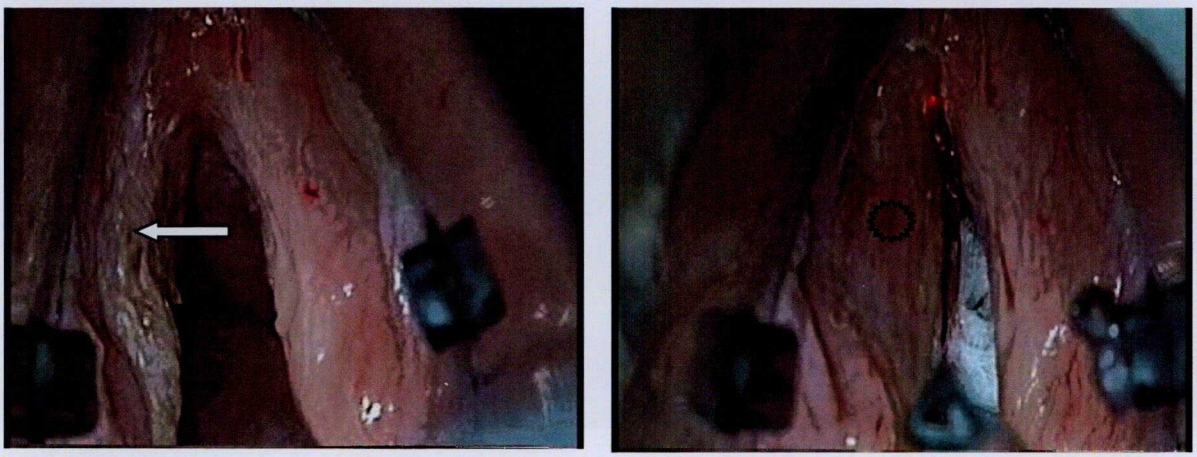
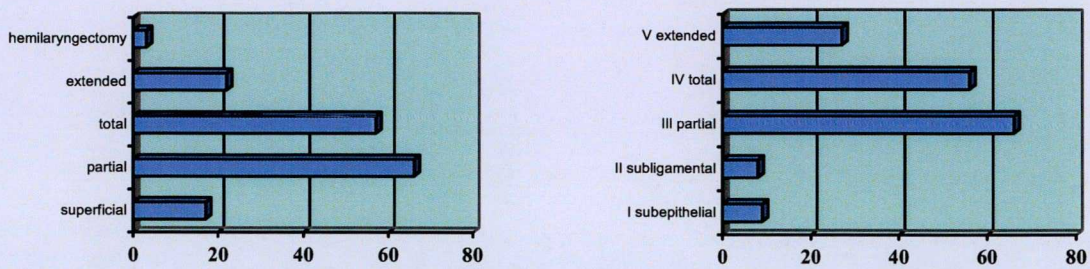


Fig.3.5. Leukoplakia (histology: in situ carcinoma) on the left vocal cord (arrow) before the operation, and the muscular layer of the vocal cord (*) after the superficial cordectomy

The excision thus corresponded to conventional microlaryngoscopic decortication of the vocal cords. Small, midcordal lesions required a "partial" cordectomy: the affected part of the vocal cord was resected completely, leaving the anterior commissure and vocal process intact. "Total" cordectomy was required when patients were found to have invasive carcinoma on one vocal cord into the vocal muscle, without impaired mobility. Tumors with anterior commissure involvement were managed by "extended" cordectomy, which included the anterior commissure down to the thyroid cartilage, the subglottic region with the cricothyroid membrane and the upper margin of the cricoid cartilage as a borderline. Larger tumors required "laser-hemilaryngectomy", a resection containing all endolaryngeal structures down to the thyroid and cricoid cartilage, the cricothyroid membrane and the ipsilateral arytenoid cartilage, and false vocal cord if necessary. The cartilaginous framework of the larynx was always left intact.

The operations on 167 patients comprised 17 superficial, 67 partial, 56 total, 22 extended and 3 laser-hemilaryngectomies. In 2000, partially on the basis of our results and

publications (11, 12) the Nomenclature Committee of the European Laryngological Society (37) officially proposed a new classification for laser cordectomy (**Fig. 3.6.**).



Our original classification

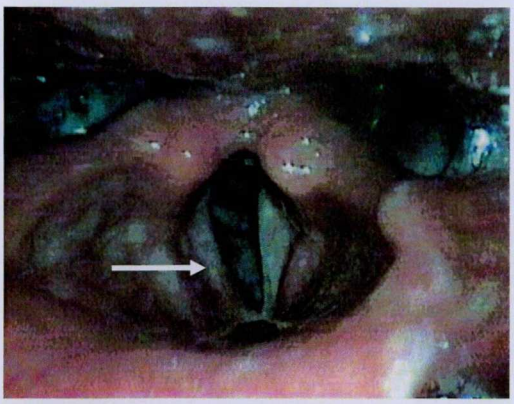
ELS classification from 2000

Figure 3.6. Subgroups of laser cordectomy

3.3.2. Perioperative morbidity and functional outcomes

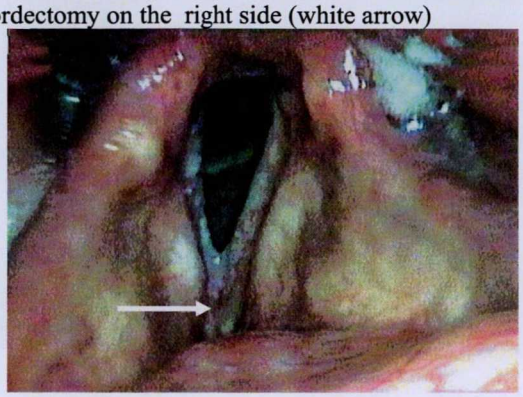
No perioperative deaths occurred in our study, and none of the patients needed tracheotomy or reintubation and nasogastric feeding tube during the treatment. In the early postoperative period, 3 cases of laryngeal edema and in 3 other patients incipient signs of perichondritis were observed. All of them were resolved by the administration of oral steroids and/or antibiotics. During the healing of the resected area, 8 (4.9%) granulomas were observed persisting for 8 to 12 weeks after the laser procedure. This granulation tissue was removed during microlaryngoscopy by the "cold technique".

The majority of the cases healed with minimal scar tissue (**Fig. 3.7.a**). Excessive scarring and subsequent laryngeal web formation or blunting of the anterior commissure was observed in 4 cases only. In 3 patients, these stenoses required further surgery to restore an adequate airway; the laryngeal web was cut and vaporized by laser, and silicone stents were placed into the anterior commissure to avoid restenosis. Blunting without functional problems was not treated (**Figs. 3.7.b-c-d.**).

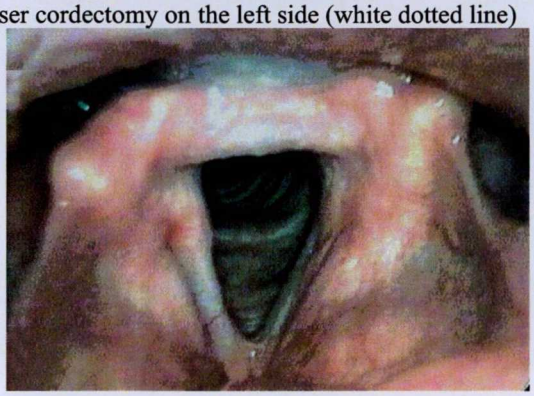


a. Minimal scar tissue formation after total laser cordectomy on the right side (white arrow)

b. Blunting of the anterior commissure after extended laser cordectomy on the left side (white dotted line)



c. Synechia in the anterior commissure (white arrow)



d. Negligible scar tissue formation after total laser cordectomy on the left side

Figure 3.7. Minor scar formations after laser cordectomies (indirect view with 90° Hopkins optics)

Detailed analysis on the voice changes following laser cordectomy was not the subject of this study and only the results on 5 patients after total cordectomy (type IV resection) are presented here. After surgery, the acoustic analysis of the voice highlighted that the mean phonation time was decreased to 6.42; fundamental frequency (F0) has been reduced to less than 130 Hz; the mean values of the examined vocal parameters were 2.54 % for Jitter, 4.01 for Shimmer and 0.36 for noise harmonic ratio (NHR) (**Table 3.1.**).

Variables	*Other laser*	*Radiotherapy*	*Our results*
MPT	14.30 ± 6.46	18.6 ± 4.4	**6.42 ± 3.11**
F0 (Hz)	169 ± 38	160 ± 43	**127 ± 28**
Jitter (%)	1.13 ± 0.85	0.93 ± 0.58	**2.54 ± 0.47**
Shimmer (%)	3.80 ± 1.60	2.81 ± 1.78	**4.01 ± 2.23**
NHR	0.41 ± 0.2	0.14 ± 0.1	**0.36 ± 0.1**

Table 3.1. Vocal function results (n=5)

3.3.2. Oncological outcome

Of the 167 patients, in 140 cases 1 laser excision proved to be efficacious to cure our patients, so the local control with initial laser treatment was 86.9 % (**Fig. 3.8.**).

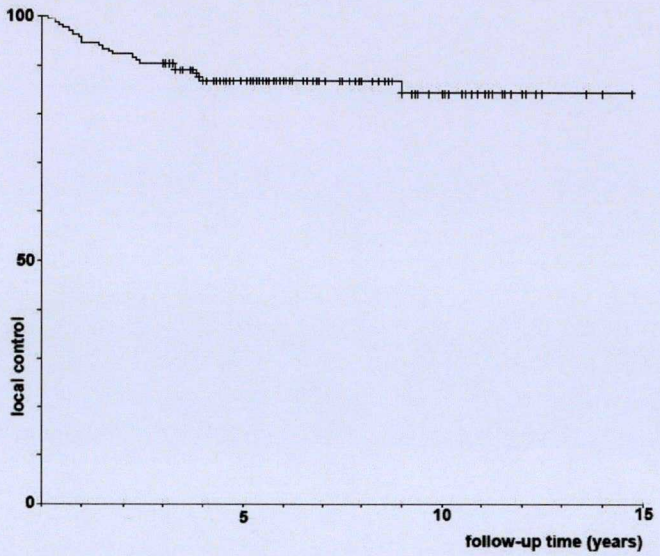


Figure 3.8. 5-year rate of local control with initial laser surgery (calculated by Kaplan-Meier method)

Local recurrence was observed in 22 patients: in 13 cases repeated laser resection, in 3 patients postoperative radiotherapy, in 4 other cases hemilaryngectomy and in 2 cases total laryngectomy were carried out. The majority of the local recurrences were manifested within 2 years after the initial laser cordectomy (mean time 21.3 months, 2-48 months) **(Fig.3.9.)**. In 1 patient from the radiotherapy group, the tumor recurred and total laryngectomy was performed; this patient was lost to follow-up. In another patient from the laser salvage group, local recurrence was observed and subsequent vertical partial laryngectomy was carried out. Postoperatively he is doing well; no signs of recurrent malignancy have been detected.

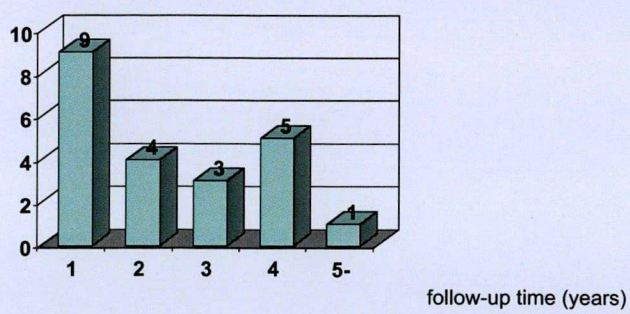


Figure 3.9. Manifestation of local recurrences after initial laser cordectomy

Thus, local control with exclusive laser treatment amounted to 94.4%, and ultimate local control with salvage for local treatment failures to 98.6%. (**Fig.3.10.**)

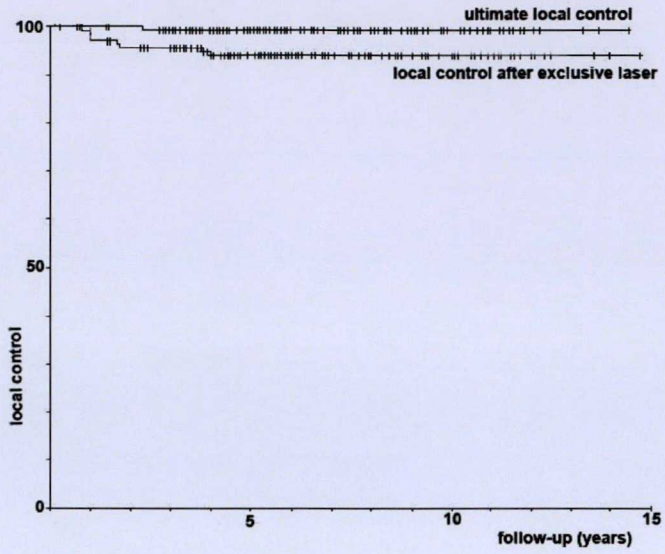


Fig.3.10. 5-year local control with laser and other salvage treatment (calculated by Kaplan-Meier method)

A total of 97.8% of the patients had their larynges preserved after 5 years (**Table 3.2.**). Lymph-node metastasis was observed in 5 patients, in all of whom modified radical neck dissection was carried out; thus the regional control was 96.4%.

Second primary tumor manifested in 12 patients (7.4%): 3 new tumors in the larynx, 3 in the oral cavity, and 3 in the esophagus, 2 in the lung, and 1 in the oropharynx.

Of the 167 patients, 25 died, 121 are alive without disease, 4 patients are alive with local recurrence, 7 patients are alive with second primary tumors, and 10 patients have been lost to follow-up within different intervals of time. 12 patients died from unrelated causes, 2 from laryngeal cancer, 4 from non-laryngeal tumors, while in 8 cases exact cause of death was unknown. The 5-year uncorrected overall survival for all 167 patients was 92.2% and tumor-specific survival was 98.9% (**Fig. 3.11.**).

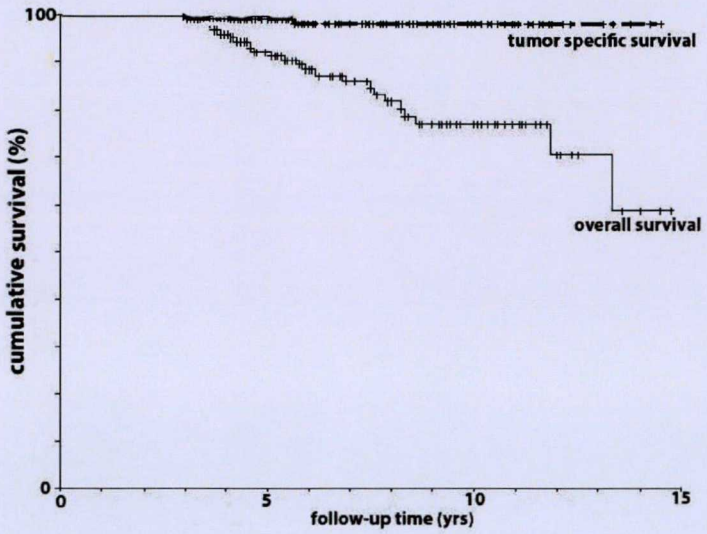


Figure 3.11. 5-year overall and tumor-specific survival (calculated by Kaplan-Meier method)

3.4. Discussion

Laser surgery represents the evolution of endoscopic surgery and, as far as the treatment of laryngeal tumors is concerned, CO_2 laser cordectomy is considered a valid alternative to other conventional methods, such as open cordectomy or exclusive radiotherapy. Very important criteria that should help in the decision between laser, conventional surgery or radiotherapy are the morbidity and possible complications of each technique.

As regards the complications of partial laryngectomy, *Giovanni* (22) conducted a study involving 127 patients who underwent partial frontolateral laryngectomy with epiglottic reconstruction for T1 or T2 glottic carcinoma. 6 patients required endoscopic laser excision of granulation tissue or adhesions, 4 patients were hospitalized for aspiration, and 1 patient required a permanent gastrostomy tube. In another study, among 81 patients who underwent a modified subtotal laryngectomy for T1–T2 glottic carcinoma *Crampette* (8) observed 7 cases of aspiration pneumonia, and 2 of postoperative glottic stenosis requiring laser, while 1 postoperative death due to a pulmonary abscess. *Spector* (42, 43) reported on 404 patients who underwent open partial laryngectomy; there were 16 with T1N0 glottic carcinoma major complications and 2 patients died. An additional 71 patients underwent open partial laryngectomy for T2N0 glottic carcinoma, 13 of whom exhibited complications including fistula, local infection, bleeding and superficial soft tissue necrosis, while 1 patient died.

Mendenhall (28) reported that 6 of 519 patients who received radiotherapy for T1N0–T2N0 glottic carcinoma developed major complications, including severe mucositis necessitating hospitalization and a treatment break, total laryngectomy for a suspected local tumor recurrence with a pathologically negative specimen, permanent tracheostomy for serious laryngeal edema and a pharyngocutaneous fistula after a salvage total laryngectomy. *Garden* (21) evaluated 230 T2 carcinomas treated by radiotherapy: 10 patients experienced severe complications, including tracheostomy, hospitalization for laryngeal edema, fistula after salvage surgery or death during or following salvage surgery.

Vilaseca-Gonzalez et al. (49) conducted a study of 102 patients who underwent transoral laser excision for T1-T2 lesions. Major complications were defined as those necessitating intensive medical treatment, blood transfusion, surgery or admission to the intensive care unit. No complication was observed in group Tis and T1 disease, while the incidence for patients with T2 disease was 13%. *Steiner* (45) investigated 159 Tis–T2 glottic carcinoma cases; only 1 patient experienced postoperative bleeding.

After laser surgery, the hospital stay is reported to be short, generally not in excess of 2-4 days and the recovery period is usually brief. In our study the mean hospital stay was 4 days, and 75 % of our patients were discharged from our clinic within a week. In a recent publication *Altuna et al.* (1) reported a cohort of 73 patients who underwent laser cordectomy as a day-case procedure. No complications related to laser surgery have been reported, and their patients stated their willingness to have further surgery in this manner if required.

In our study no major complications, such as bleeding, no perioperative death were observed. Reintubation or tracheotomy was not required to maintain the safe airway after laser surgery. All of our patients were able to eat and drink without aspiration even after extended cordectomy, so nasogastric feeding tube insertion was not needed. As a minor complication, minimal edema and signs of incipient perichondritis was observed in 3 % of the patients in the early postoperative period. In the late postoperative period, which is considered approximately 6 weeks after the first intervetion and when the re-reepithelization of the operated glottic region is finished, granuloma formation, scarring and blunting of the anterior commissure was encountered in 4 % of our patients only. In connection with the complications and morbidity of the different treatment methods, it can be clearly seen that laser cordectomy offers the lowest complication rate and causes minimal morbidity.

To obtain a good voice quality is also a very important cornerstone of vocal cord

cancer treatment. *McGuirt* (27) and his group evaluated the voice outcome 6 months after radiotherapy or laser cordectomy. All patients were free of disease after treatment, and the laser treatment group had undergone resection of less than half the cordal depth. Both the physician- and patient-rated voice outcomes were better after radiotherapy as compared with transoral laser excision, but speech pathologists detected no differences in the results. Voice quality after transoral laser excision is closely associated with the type of the resection, the extent of resection, the conformation of the neocord, the individual scar reaction and the glottic or supraglottic compensations performed by the patient in order to compensate the glottic insufficiency. This was demonstrated in a study by *Delsupehe* (14), he reported on perceptual voice analysis in which 12 patients treated with radiotherapy were compared with 30 patients who underwent narrow margin laser cordectomy. Although the voice quality deteriorated initially after surgery as compared with radiotherapy, no significant differences were detected at the 6-month or 2-year follow-up.

Our observations and the results of the acoustic voice analysis performed on a small sample of our patients (**Table 3.1.**) clearly showed that type IV (formerly extended) cordectomy led to more scarring and thus worse voice quality (with the characteristics of a breathed voice), compared with less extensive resection types. This alteration of the voice gradually improved in time and the majority of our patients live normally without any disturbance in their everyday verbal communication, and they are generally satisfied with their voice quality.

The analysis of comparative costs of radiation therapy and laser surgery was the main topic in several studies (5, 19, 23, 32). In the study by *Myers* (32), the costs of treating patients with T1 glottic carcinoma, including the management of recurrences were found to be a total of 1.5 million dollars per 100 patients compared with 3.9 million dollars per 100 patients for radiation treatment. *Foote and Brandenburg's* calculations showed radiation therapy to be 1.4 times as expensive as laser treatment (5, 19). The finding that laser surgery is a more cost-effective treatment modality is supported by the investigations and results of our team, too (39). If we consider that the analysis did not take into account indirect costs, such as missed work for those who were employed, the true difference is much higher and in this respect laser surgery is the more economical as the treatment can be done during a short hospital stay, whereas radiation therapy lasts for 5-6 weeks.

Radiotherapy remains the treatment of choice even today for early glottic carcinoma in the USA, Canada, United Kingdom and northern Europe. Its main advantage is voice preservation, provided initial treatment is successful. However, the local control rates with radiotherapy as the initial treatment range from 86% to 94% for lesions classified as T1, and from 64% to 77% for T2 lesions (21, 28, 29) (**Table 3.2.**). In the Mediterranean area, e.g. in Italy, France or Spain, mainly following the "French laryngeal surgery methods", vertical or subtotal partial laryngectomy is preferred. Some publications have reported local control rates of 90-95% for vertical partial procedures and supracricoid partial laryngectomy for T1a, and 70-90% in cases of T2 tumors (18, 25, 31) (**Table 3.2.**). Local control rates after laser excision range from approximately 85% to 98% for T1 disease and from 70% to 85% for T2 disease, while the ultimate local control rates range from 90% to 95%. Local control with laryngeal preservation generally exceeds 95% for patients with T1 malignancies (16, 20, 34, 35) (**Table 3.2.**).

					5-year local control (%)		*5-year survival (%)*	
Author, year	**Treatment**	**Follow-up time**	**No of pts.**	**Tumor**	**Local control**	**Larynx preservation**	**Overall**	**Tumor specific**
Eckel, 2000	Laser	mean 4.5 yrs	285	Tis-T2	98	94	71	99
Steiner, 1993	Laser	median 6.5 yrs	159	Tis-T2	94	99	87	100
Gallo, 2003	Laser	minimum 3 yrs	12	Tis	100	100	93	98
			120	T1a	94	100	94	97
			24	T1b	92	100	84	97
Our cases	**Laser**	**minimum 3 yrs**	**167**	**Tis-T2**	**94**	**98**	**92**	**99**
Spector, 1999	PL	minimum 3 yrs	404	T1	92	93	92	97
Thomas, 1994	PL	median 6.6 yrs	159	Tis-T1	93	94	84	NA
Spector, 1999	PL	minimum 5 yrs	71	T2	93	93	NA	92
Mendenhall, 2001	RT	minimum 2 yrs	230	T1a	94	95	82	98
			61	T1b	93	95	78	98
Garden, 2003	RT	median 6.8 yrs	230	T2	72	NA	73	92

PL=partial laryngectomy, RT=radiotherapy, NA=not available

Table 3.2. 5-year local control and survival data of laser cordectomy, partial laryngectomy and radiotherapy

Our long-term oncologic results clearly demonstrate that we achieved results as concerns the rates of local tumor control, overall and tumor-specific survival or larynx preservation that were similar to or better than the rates of radiotherapy or open partial surgery. In our cases, one laser intervention was sufficient to cure 87 % of our patients. This cure rate mounted to 94 % with exclusive laser surgery (initial laser + salvage laser) while the final local control (exclusive laser + other salvage) achieved 97 %. In 97 % of our cases we succeeded in preserving the larynx. These results are similar to some other representative

laser cordectomy studies, and better than the rates of open cordectomy or radiotherapy.

Analyzing the survival data of different studies it can be concluded, that 6-29 % of the patients die of intercurrent disease within 5 years of treatment, while tumor-related death is seldom seen (**Table 3.2.**). In our study 15 % of our patients died, but only 2 patients had primary cancer-related causes. The other cases of mortality were due to the cardiovascular diseases, advanced age, general health status or the high incidence of second primary tumors. Hence, special attention should be paid to the importance of an extended and careful follow-up, since second primary tumors may occur at any time after the initial diagnosis.

Our team proved with the previously published papers (IV), presentations on different scientific meetings and congresses (VIII, IX, XII, XIII) and the results of this study on the biggest Hungarian cohort of patients, - which can be regarded as an important study among the notable international studies-, that laser cordectomy is safe, minimally invasive, and allows an additional surgical line of treatment. It has very low morbidity, minimal complications and an affordable cost-effectiveness; its oncologic results are similar or better than the other conventional treatment. A decade ago our opinion was more cautious, laser-cordectomy was proposed only as one option among other treatment modalities, if close follow-up and „salvage"-therapy (radiotherapy, open partial laryngectomies, etc.) were available, while today we emphasize that laser cordectomy should be the first choice of treatment for early vocal cord carcinoma. Thus, the laser cordectomy is no longer a treatment modality restricted to highly selected patients, but is a real alternative to radiotherapy or open cordectomy as a primary treatment for early carcinoma of the glottis.

4. AUTOFLUORESCENCE VIDEOENDOSCOPY FOR THE DIAGNOSIS AND TREATMENT OF PREMALIGNANT AND EARLY MALIGNANT VOCAL CORD LESIONS

4.1. Introduction and background of autofluorescence imaging techniques

Head and neck squamous cell carcinoma presents a major problem in all European countries, and accounts for approximately 5% of all noncutaneous malignancies. Despite advances in surgical techniques and other combined oncologic treatments, the 5-year survival rate has stayed at approximately 50% for all stages of disease over the past 30 years. The main reasons for this poor outcome are the delayed diagnosis during the primary tumor staging procedure, and the high incidence of second primary tumors in patients who have already been treated for head and neck carcinomas (12, 18). The early detection of cancers allows less aggressive treatment and may promise a greater chance for the long-term survival (23).

Head and neck tumors are characterized by a tendency to field cancerization with multicentric tumors. The concept of field cancerization suggests that repeated exposure to carcinogens such as alcohol and tobacco causes damage to wide areas of the mucosa in the upper aerodigestive tract, leading to multiple independent neoplastic and preneoplastic lesions (25). This multistep process and field cancerization provide a unique challenge for the detection of precancerous lesions. Early malignancies of the upper aerodigestive tract are usually diagnosed by visual identification, which relies basically on the clinical experience of the examiner in recognizing suspicious lesions during the physical examination. However, the detection of these early-stage lesions may be difficult during conventional endoscopy with white light, as the lesions can sometimes be indistinguishable from the more common benign inflammatory conditions.

For better visualization of the lesions, topical staining with supravital dyes has been exhaustively studied. These staining techniques have not been widely accepted as a routine clinical screening method, because of their rather complicated application procedures (20, 22).

Human tissues contain a number of natural molecules that can fluoresce in ultraviolet and visible light. These endogenous fluorophores include riboflavins, tryptophan, collagen, nicotinamide and porphyrins (**Fig. 4.1.**).

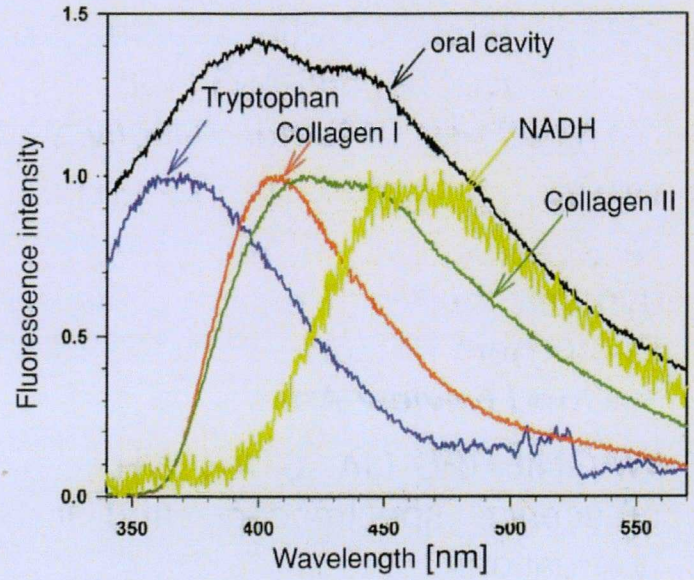


Figure 4.1. Fluorescence spectra for different pure substances in comparison with the squamous epithelium of the oral mucosa

When the mucosal surface is illuminated by light, the light can be reflected, back-scattered or absorbed, or induce cellular autofluorescence (AF). The first three optical properties, which are known as reflectance imaging processes, are used during conventional white light examinations. The detection of AF is rather difficult, because of its very low intensity and back-scattered light. The fluorescence characteristic profile of tissues depends on their biochemical composition and histological structure. During malignant transformation, the morphological alterations in premalignant and normal tissues produce AF spectral changes, which were initially only detectable by spectrofluorometry (8, 10, 11, 13, 21). Fluorescence spectroscopy comprises is the detection and analysis of the difference in wavelength between the excitation light and the re-emitted fluorescent light. Later fluorescence spectroscopy was developed into a fluorescence imaging technique. For the amplification of weak fluorescence signals, special cameras equipped with either image intensifiers or time integration facilities were included. These modifications finally resulted in real-time images, suitable for clinical use (**Fig. 4.2.**). This system, when incorporated into standard endoscopes, allows the screening of a large surface of the mucosa during endoscopic examinations (9, 13, 24).

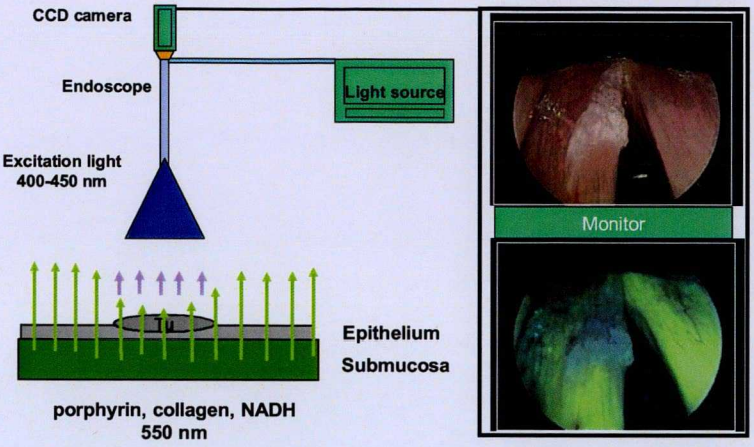


Figure 4.2. AF imaging technique

Palcic et al. developed the LIFE (laser induced fluorescence endoscopy) system (Xillix Technologies Corporation, Canada), using the excitation light of a helium-cadmium laser (442 nm), which focuses on the detection of the fluorophore protoporphyrin IX. They demonstrated that this new technique is at least twice as sensitive as white light endoscopy for the detection of carcinoma in situ (19). The results of AF endoscopy were evaluated in a large number of patients and this technique proved to be of great value in the detection of early lung cancer, thereby becoming generally accepted by physicians (14, 15). After this encouraging pulmonology application, multiple publications reported on its clinical applicability in the diagnosis of head and neck malignancies, mainly in laryngeal localizations (5, 6, 26).

The Storz Company, using a xenon light source with a band of excitation wavelength from 375 to 440 nm, and producing AF images in a green spectral range, has developed a less expensive device, the D-Light AF System (1, 7). With this system, *Betz et al.* evaluated the AF imaging method alone, and combined with induced fluorescence for the better delineation of oral tumors (2), while *Malzahn et al.* reported their observations on AF endoscopy in the diagnosis of precancerous and cancerous laryngeal lesions in 111 patients (17).

In Hungary, *Csanády et al.* (3) from Szeged, and *Csokonai Vitéz et al.* from Budapest (4) published their results with 5-ALA induced protoporphyrin fluorescence endoscopy, while

paper about the use of autofluorescence videoendoscopy was published first by *Paczona et al.* (V, VI).

The aim of the present chapter is to evaluate the feasibility and discuss the diagnostic potential of AF videoendoscopy as a complementary visual aid in the routine endoscopic diagnosis of early glottic lesions.

4.2. Adaptation of the AF method to keratinized lesions of the vocal cords

In our prospective study, 52 patients (42 men and 9 women) with signs or symptoms suggesting head and neck cancer underwent panendoscopy under general anesthesia from November 2001 to April 2003 in the Department of Otorhinolaryngology, Head and Neck Surgery at the Gustave-Roussy Institute and the University of Szeged. The age of the patients ranged from 34 to 82 years (mean 57.3). Among them, 41 displayed laryngeal lesions, and 8 pharyngeal and 3 oral lesions for control. Statistical analysis was performed only in those 44 cases with suspected precancerous or cancerous lesions (33 laryngeal, 11 oral or pharyngeal localizations), while 8 macroscopically benign laryngeal lesions were excluded (Reinke edema, granuloma, papilloma, cordal cyst, and polyp).

The blue light source was provided by a xenon short arc lamp with an excitation wavelength ranging from 375 to 440 nm (D-Light/AF Light System, 20133301-1). The camera system was a target-integrating high-resolution color charge-coupled device (CCD camera, Tricam SL-PDD, 202210 70; Karl Storz Company). This camera was connected to different-length rigid telescopes (Straight Forward Telescope 0° and 30°; 8700 DA, 8710 AA, 8707 DA; Karl Storz Company). This system allows real-time white light endoscopy and switches over to AF endoscopy with the press of a footswitch. At the beginning of the study, the findings were recorded for documentation and further analysis on video tape by a Sony videocassette recorder (model SVD-9500 MDP). Photographs were taken by Sony digital still recorder (model DKR-700 P) and printed by Sony color video printer (model UP 2300 P). Later, all these functions were integrated into a laptop computer (Inspiron 8200, Dell Computer) by a video capture card (VCE-B5A01, ImperX Inc., USA).

All areas of the upper aerodigestive tract were first inspected by the examining ENT surgeon under conventional white light, and all suspicious mucosal lesions were carefully documented as to macroscopic appearance and superficial extension. Next, after the switch-over to fluorescence excitation light, AF images were recorded.

In each case, tissue samples were taken. The specimens were routinely fixed in 4% formalin. After the usual process of embedding the tissue samples in paraffin blocks, step-serial sections were performed and assessed by a qualified local histopathologist.

Grouping macroscopically by typical surface appearance, 8 benign lesions (3 of Reinke edema, 2 of granuloma, 1 of vocal fold polyp, 1 of intracordal cyst and 1 of papilloma), 6 leukoplakia (4 of epithelial hyperplasia and 2 of moderate dysplasia) and 38 tumor suspect exulcerated and keratinized cases (35 cases of invasive squamous cell carcinoma, 3 carcinoma in situ) were found.

In the larynx, all lesions were localized in the glottic region, 29 lesions proved to be histologically precancerous or cancerous, while 12 cases were benign **(Table 4.1.).**

Laryngeal pathology	**AF characteristics**	
	Positive (blue or violet)	*Negative (bright-green)*
Benign lesions (8)	4	4
Leukoplakia (6)	2	4
Tumor suspect cases (27)	26	1
	32	**9**

Table 4.1. AF characteristics of laryngeal lesions (n=41)

4.3. Results

All lesions were visible on white light and AF endoscopy. The normal mucosa appeared green on the acquired images, while the neoplastic tissue yielded lower AF intensities in general. The malignant lesions were therefore demarcated from the adjacent normal mucosa by a reddish-blue to violet color (**Figs. 4.7. and 4.8.**).

4.3.1. Laryngeal localization

4.3.1.1. Benign lesions

The normal mucosa showed a normal green fluorescence (**Fig. 4.5.**). In Reinke's edema, we did not recognize any change in the typical green fluorescence (**Fig. 4.4.**).

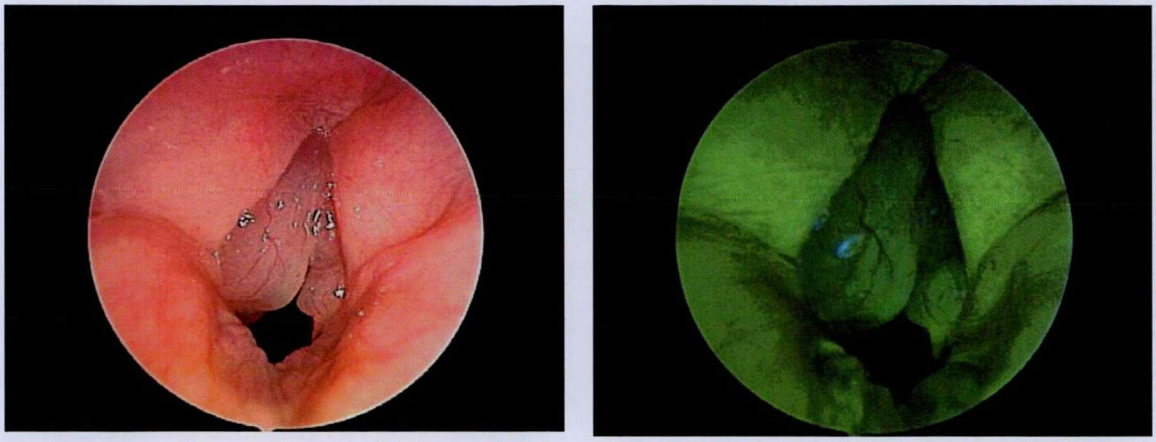


Figure 4.4. Bilateral Reinke's edema on the vocal cords

Some benign lesions, such as granulation tissue, papilloma (**Fig. 4.5.**) and vocal fold polyp also displayed a loss of green fluorescence.

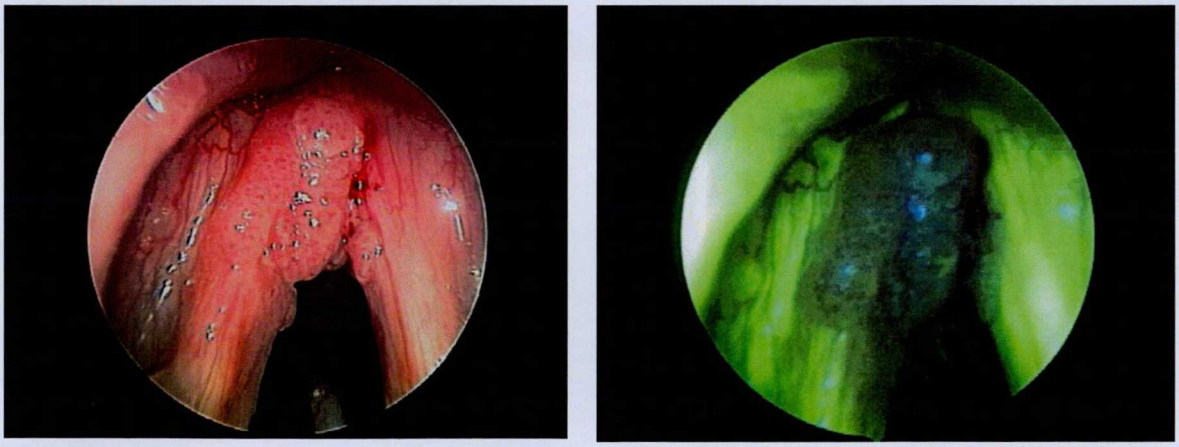


Figure 4.5. Papilloma involving the anterior commissure, right vocal cord displayed normal green fluorescence

4.3.1.2. Precancerous and cancerous lesions

Keratinized lesions such as leukoplakia, in some cases showed a normal green fluorescence, or when marked hyperkeratosis was present, it displayed light-green or white color, depending on the thickness of the mucosal alteration (**Fig. 4.6.**).

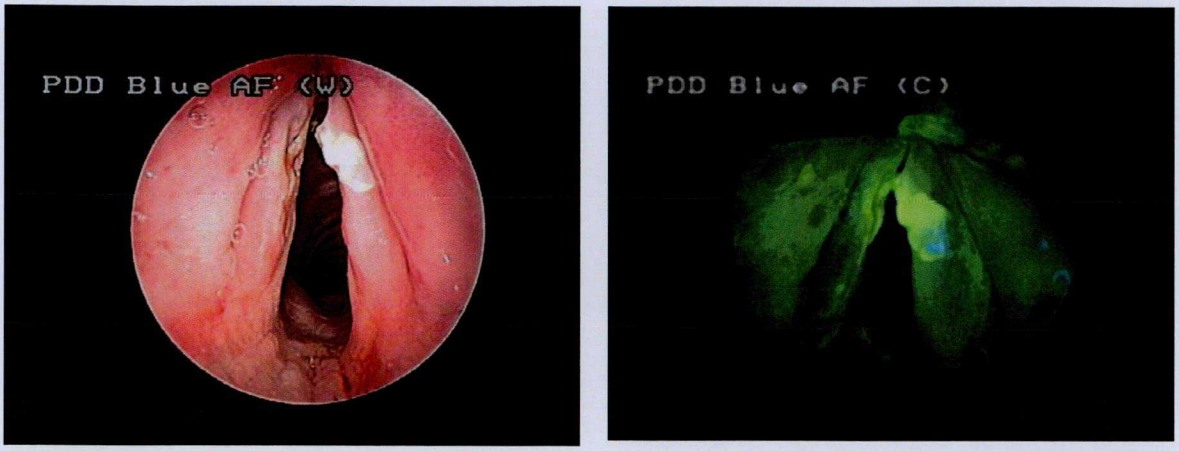


Figure 4.6. Leukoplakia on the right vocal cord (histology showed simple keratosis without any dysplasia)

In other cases the leukoplakia gave a clearly recognizable altered green fluorescence with a shift to reddish-blue, violet fluorescence. After switching several times between white light and AF imaging modes, these areas were sometimes also recognizable during white light imaging. The delineation could be either sharp or slightly blurred (**Fig. 4.7.**).

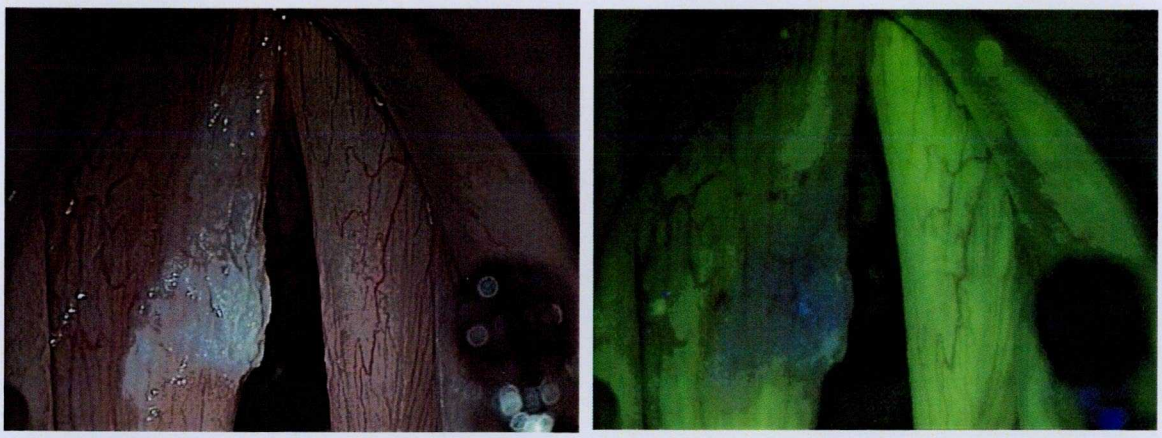


Figure 4.7. Leukoplakia on the left vocal cord (histology revealed moderate dysplasia)

Macroscopically tumor suspect, exulcerated and keratinized cases, such as in situ or infiltrating carcinoma all displayed a marked altered green fluorescence, presenting a reddish-violet color. Only 1 case with excessive hyperkeratosis proved to be false-negative, when the thick keratin layer gave whitish-green fluorescence, masking the underlying basal cell layers with invasive carcinoma. In all cases, the border of the lesions was more extensive than

expected from the white light images, as a result of the dysplastic epithelium around the infiltrating carcinoma (**Figs. 4.8-4.10.**).

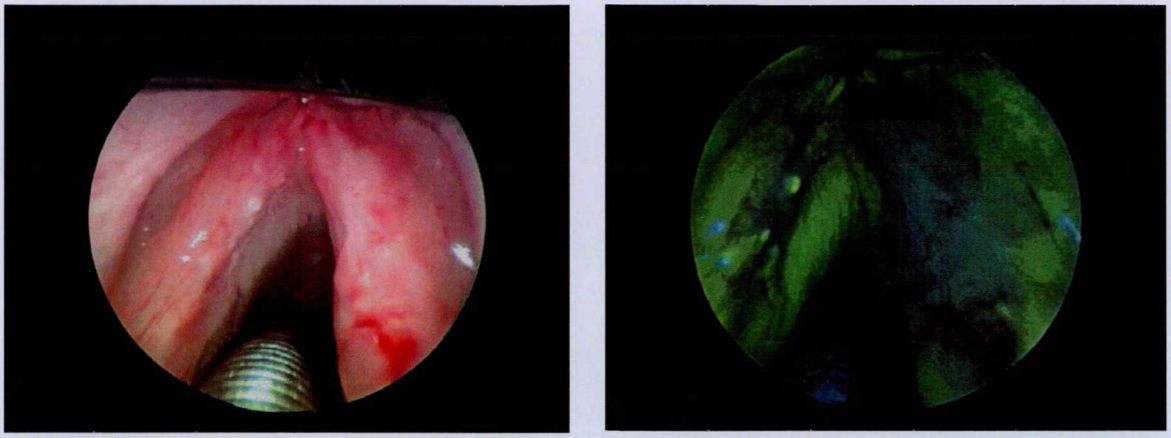


Figure 4.8. Invasive carcinoma on the right vocal cord, AF helped to delineate the tumor borders on the right side

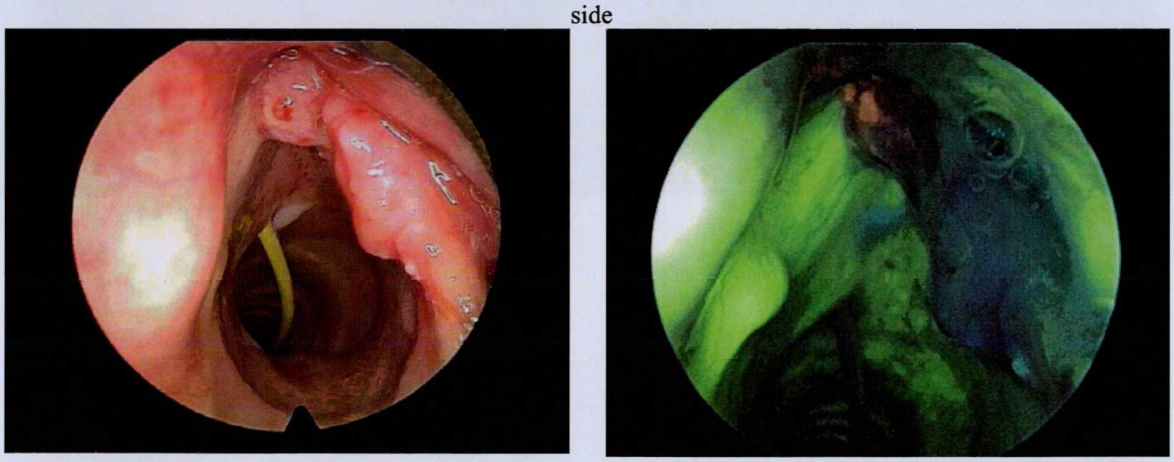


Figure 4.9. Invasive carcinoma on the right vocal cord invading the anterior commissure

Figure 4.10. Invasive carcinoma on the right vocal cord. Dysplastic area around the tumor was better visualized during AF endoscopy (arrows)

In 13 cases with T1a tumors, if the tumor extension allowed oncologically safe curative treatment, endoscopic CO_2 laser resections were performed. The exact border of each lesion was assessed by careful videoendoscopy, switching over from white light to AF mode and back several times until the resection line could be determined. After the completed resection, the surgical margins were controlled with the AF method (**Fig. 4.11.**). In the event of a suspected residual tumor or an abnormal mucosal surface, a more extensive excision was performed. In 2 cases, AF revealed an abnormal area near the resection margin; in both, the histology indicated severe dysplasia.

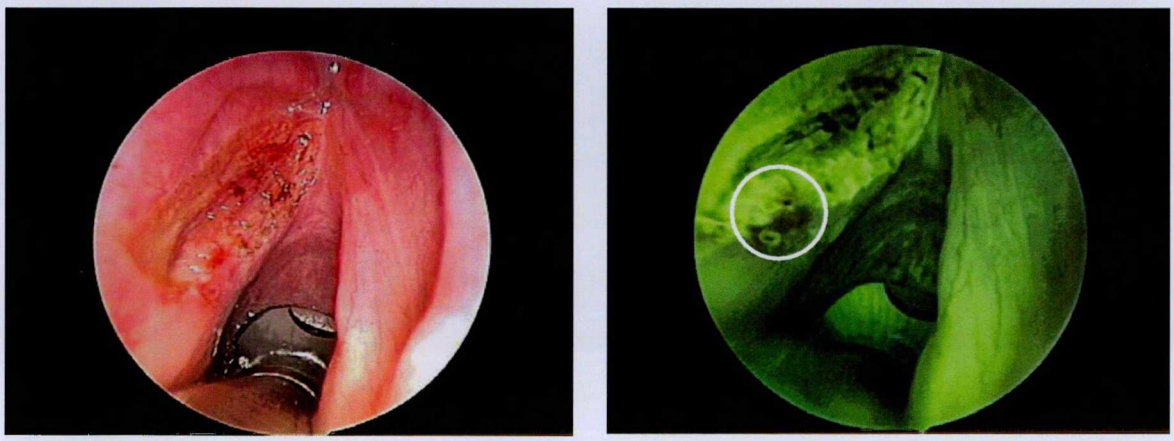


Figure 4.11. Laser cordectomy on the left side. AF revealed a dysplastic lesion close to the resection margin (white circle). The histology indicated severe dysplasia

In cases of more advanced tumors, only multiple biopsies were taken for histological evaluation.

4.3.2. Adaptation of the technique to oral or pharyngeal localizations

All lesions were detectable under white light and AF endoscopy and proved to be invasive carcinomas histologically. All tumors exhibited the typical loss of green fluorescence, yielding a more or less accentuated reddish-blue color. Similarly to the above-mentioned laryngeal cases, in 3 patients with oropharyngeal tumors, the lesions were found to be more extensive on AF endoscopy than expected after white light endoscopy (**Fig. 4.12.**).

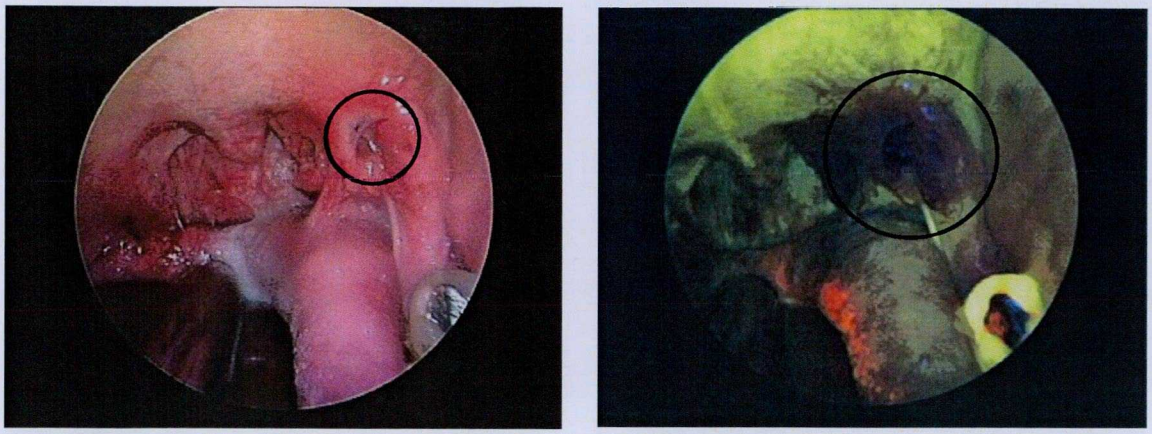


Figure 4.12. Infiltrative carcinoma in the left tonsillar region (circle). AF showed a more extensive lesion than expected after white light endoscopy

In 2 patients, one new additional lesion was detected only by AF endoscopy. In 1 case, severe dysplasia was diagnosed pathologically, while in the other case moderate dysplasia of the oropharyngeal mucosa was revealed (**Fig. 4.13.**).

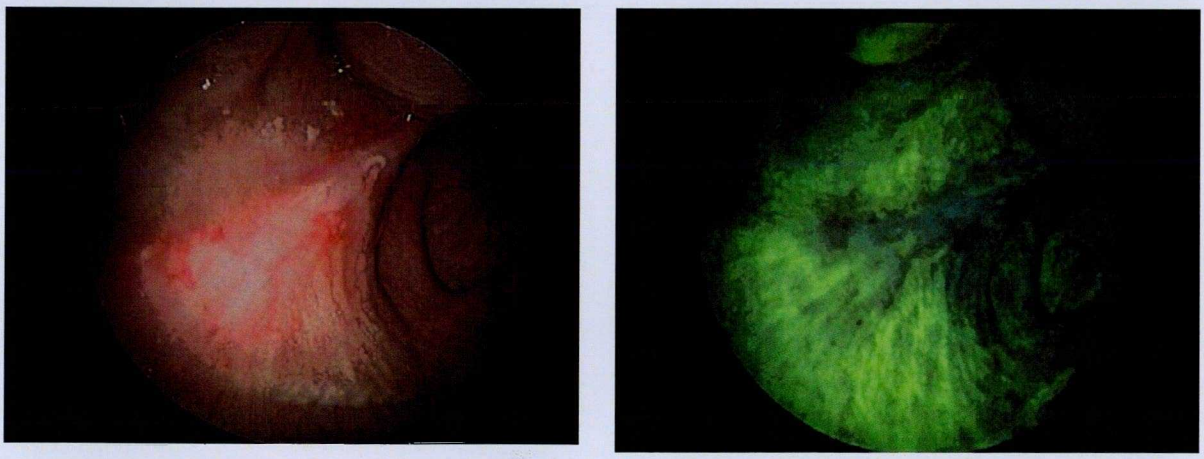


Figure 4.13. Whitish plaque (moderate dysplasia) on the left anterior faucial pillar was barely recognizable on white light, but AF allowed a better delineation

Under histopathological control, our AF videoendoscopic method achieved a sensitivity rate of 97.4% and a specificity rate of 75.2% (**Table 4.2.**), and 2 additional new lesions were detected by AF alone. One false-positive and one false-negative diagnosis resulted from different degrees of hyperkeratosis in 2 different cases.

		Histology	
	n=44	*Cancerous*	*Noncancerous*
AF videoendoscopy	*Cancerous*	39*	1
	Noncancerous	1	3**
		40	**4**

Table 4.2. Histopathologic versus AF videoendoscopy characteristic in the diagnosis of suspected laryngeal, oral and pharyngeal cancerous lesions (*sensitivity: 97.4%; **specificity: 75.2%).

4.3.3. Pitfalls of the AF technique

Bleeding from ulcerated tumors due to accidental injury on insertion of the endoscope can influence the assessment of AF imaging because of the high absorption of the exciting light by the heme molecule (**Fig. 4.14.**).

Figure 4.14. Blood absorbs the exciting light strongly, masking the underlying lesion (arrows)

In some cases, bacterial colonization was observed on the ulcerated necrotic surface of tumors, reflecting as orange or yellow bright fluorescence under the exciting light. This variation of the AF color was always clearly distinguishable from the true neoplastic fluorescence. This pattern of color was also observed on the back surface of the tongue (**Fig. 4.15.**).

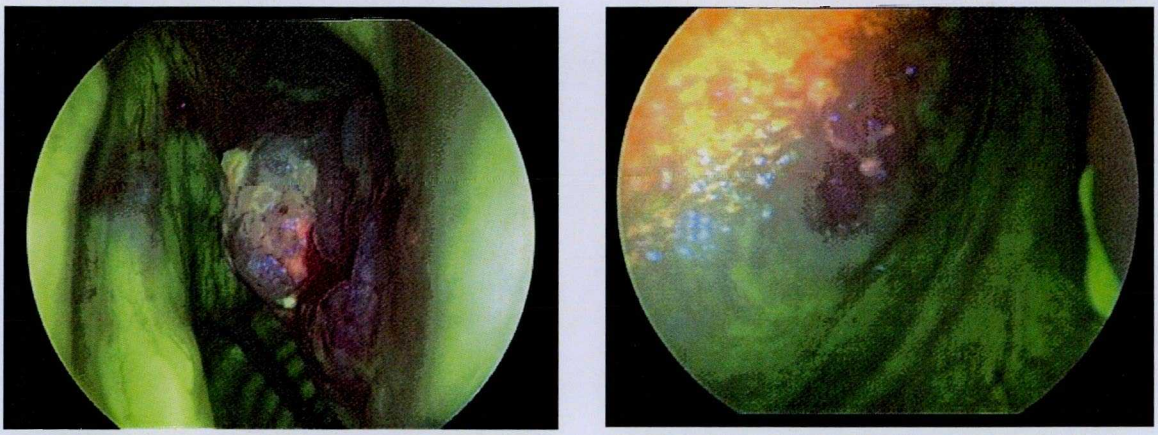


Figure 4.15. Bacterial coating on the necrotic surface of a T2 glottic cancer (red spots, left picture), and on the back of the tongue (yellow spots, right picture)

4.4. Discussion

Under AF videoendoscopy, the healthy mucosal areas of the head and neck regions displayed a typical bright-green color. This fluorescence was of almost the same intensity, but in certain regions, such as the surface of the vocal cords or the hard palate, significant differences could be observed. The phenomenon was even more intense after superficial laser resection of the vocal cords, when the covering mucosa was excised, and the vocal ligament was more superficial (**Fig. 4.11.**). This high fluorescence intensity was emitted by the elastic fibers of the lamina propria. When the elastic fiber was replaced by the less fluorescent collagen, a significant fluorescence intensity decrease was observed, as in the case of scar tissue after endolaryngeal surgery or after irradiation of the larynx (17).

The AF appearance of premalignant lesions was found to vary. These mucosal alterations are characterized by the production of keratin (keratosis). Most often, these lesions macroscopically manifest as whitish-gray "spots" on the surface of the degenerated mucosa. They usually emit very strong light-green fluorescence, which is sometimes even brighter than that of the normal mucosa. If there are no other fluorescence signs with which to recognize the underlying malignant transformation, such as surrounding violet or reddish-blue spots, these lesions can be overlooked, as a benign finding. In our study, 2 epithelial hyperplastic laryngeal lesions were observed, one a false-negative and one a false-positive case, highlighting the insufficiency of the method in the differentiation of such lesions. However, the 2 additional new premalignant lesions (severe and moderate dysplasia), detected only by AF, indicate the possible application of the method as a regular screening procedure in a high-risk population.

The AF image of cancer was less variable in most of the cases, being recognized as a violet, or reddish-blue color. The glottic region was more favorable for accurate AF delineation than the oral and pharyngeal regions. Moreover, smaller, flat superficial epithelial lesions were found to be better outlined by AF photodiagnosis than large, ulcero-infiltrative tumors. The demarcation of these lesions provided a sharp, good image quality, but often revealed a greater size than expected from white light examination, indicating the structural changes in the dysplastic mucosa around the infiltrating tumor (**Fig. 4.10.**).

In 4 cases we found that certain benign lesions of the larynx, such as papillomas, granulomas or polyps, also display a loss of green fluorescence. This may be the result of the enhanced content of coiled and dilated blood vessels, which absorb the excitation light, as well as the presence of inflammatory cells. Theoretically, these false-negative cases can reduce the sensitivity of the AF endoscopy method, if it is used alone without white light evaluation, but this is seldom the situation in clinical practice. Moreover, these benign laryngeal lesions present several other evident macroscopic properties indicating their benign character, and therefore the correct diagnosis can be easily reached.

Bacterial overgrowth produces exogenous fluorophores (e.g. protoporphyrin IX) that may influence the AF characteristics of the underlying mucosa. This exogenous fluorescence signal can reduce the clinical applicability of AF endoscopy, especially in cases of lingual malignancies (17). In our cases, these bright-yellow or red fluorescence signals were also observed on the back of the tongue, on the gingival plaques and teeth, and on the necrotic parts of malignancies (**Fig. 4.14.**). In our series, 2 patients with lingual cancer were detected, and the above-mentioned bacterial colonization on the back surface of the tongue did not influence the evaluation of these lesions. The bacterial coatings on the necrotic surface of advanced tumors were more often visible, as spotted yellow or red particles, without any significant influence on the tumor delineation.

Other endogenous fluorescence substances, such as oxygenated hemoglobin, can greatly influence the AF signals during videoendoscopy. In the event of bleeding, the absorption of the exciting light by blood, can greatly affect the evaluation of tumorous lesions (**Fig. 4.14.**). In our study, special care was taken to avoid unnecessary bleeding. Hence, for the ventilation of our patients, intercrico-thyroid high-frequency jet-ventilation was used instead of transoral/transtumoral intubation. If, despite all precautions, some bleeding did

occur, hemostasis was secured with the local application of a vasoconstrictor solution, such as adrenalin.

Our results demonstrated a sensitivity of 97.4%, and a specificity of 75.2%. The sensitivity is very good, but specificity should be increased. To differentiate between the different degrees of dysplasias and beginning cancerous infiltration mainly in the diagnosis of laryngeal cancer, a possible strategy could be supplementation of the AF technique with contact endoscopy (1, 17). To improve this moderate specificity, another promising solution may be combination of the AF method, with protoporphyrin IX-induced fluorescence endoscopy. After local application of an exogenous fluorescent inducer, such as 5-aminolevulinic acid (5-ALA) or its derivatives, the fluorescence contrast of the premalignant or malignant lesions can be significantly enhanced in the red spectral area, with detection as a bright-red fluorescence signal (3, 4, 16).

In cases of small superficial glottic lesions, careful AF assessment of the lesion borders was performed and if the extent allowed an oncologically safe endoscopic resection, CO_2 laser excision of the affected vocal cords was carried out. After each operation, the surgical margins were systemically controlled by the white light, and AF method. The borders of the resections were clearly visible on AF endoscopy. If the photodiagnosis showed an altered fluorescence signal, different from the healthy light-green color, surgery was repeated, with excision of a wider mucosal area (**Fig. 4.11.**). Although our series includes only a small number of patients treated by endoscopic laser surgery, this clinical application of the D-Light AF System seems to be a very promising method in the intraoperative control of surgical margins.

Although microlaryngoscopy is the standard method in the diagnosis and treatment of glottic precancerosis and early cancers, there is still a need for improvement of our pre- and intraoperative assessment. Our results showed that AF videoendoscopy enables laryngologist to distinguish between benign lesions and precancerous epithelium with a very high sensitivity rate, and the demarcation of the lesions can be intensified by the color contrast (V, VI, XI, XIV). Our surgical concept has been modified, and we used AF videoendoscopy for intraoperative control of surgical margins after the endoscopic CO_2 laser resection of glottic cancer. The detection of additional lesions, invisible on conventional white light endoscopy, clearly illustrates another possible use of this method, for the follow-up of treated patients, or in the routine screening of a high-risk population for precancerosis or tumorous lesions.

CONCLUSIONS

In 1994, when I started to work as a young resident doctor at the ENT Clinic in Szeged, I had the opportunity to join the laryngeal oncologic microsurgery team coordinated and managed by Professor Jenő Czigner. In that year, the clinic organized the first Hungarian endolaryngeal surgery workshop under the leadership of Professor Oscar Kleinsasser, the "doyen" of laryngomicrosurgery. His presence and meaningful participation were a very memorable to all those attending. Personally I was highly impressed. I took an active part in the preparatory work including to design and preparation of the necessary prototype of a cadaver larynx holder. This holder provides an inexpensive platform, which is easily constructed from readily available materials. Use of this device independently or in a small group is of value in good educational feedback-oriented programs, similar to well- established temporal bone dissection courses. Although there is certainly no substitute for a real patient, the holder can provide an effective means of acquiring surgical skills in endolaryngeal surgery. This training apparatus can facilitate endolaryngeal surgical instruction and can help establish clinical competence in laryngology in residency training and continuing medical education. Since 1994, this simple model has proved to be a unique and very useful tool. It has been tested and utilized in a local institution and in many advanced international laryngeal surgery courses, and perfectly fulfils the purposes for which it was designed.

In 1995, the European Laryngological Society (ELS) was founded. In recognition of our clinic's scientific contribution in the field of laryngology, Professor Czigner was elected a member of the scientific committee, and our team was requested to present several papers at the first scientific meeting of the ELS in Marburg. I took again an active part, in the retrospective analysis of the results of treatment of glottic precancerosis by laryngomicrosurgery. The results of my clinical studies of glottic precancerosis based on 18 years of experience lend themselves to further considerations. The number of hospital-based laryngeal precancerosis cases has not increased in the last 18 years. Among the etiologic factors, no major changes can be observed. Glottic precancerosis undoubtedly has the potential to develop into invasive carcinoma, and patients with a higher grade of dysplasia have a much greater likelihood of developing cancer than those presenting with keratosis without dysplasia or mild dysplasia. The incidence of cancer development can be decreased through the appropriate use of endolaryngeal laryngomicrosurgery coupled with CO_2 laser techniques. Long and careful follow-up is mandatory since malignant transformation may

occur even many years after the initial diagnosis. It may be concluded from our cases that radiotherapy and/or open laryngeal surgery can be regarded as "overtreatment" in cases of carcinoma in situ. Our experience and data clearly demonstrate that most vocal cord cancers cannot be assessed simply as a progression of the precancerous lesions; it is likely that there are other factors besides those already known that can influence the progression of the disease. If we compare the rate of malignant transformation of glottic precancerosis and the incidence of glottic cancer, it is obvious that the pathway from keratosis with atypia to invasive carcinoma is observed more rarely than the occurrence of glottic cancer itself. This would explain why lesions of the same grade develop into carcinoma only in certain patients, and why lesions of lower grades can develop into malignancies without passing any of the intermediate stages. Studies on the subcellular changes and oncogenes of tissues exhibiting dysplastic lesions can yield further evidence on these aspects, indicating whether they will turn malignant or not.

In the late 1990s, my scientific interest gradually turned toward endoscopic laser surgery. After becoming familiar with the new CO_2 laser surgery method, our team conducted several surveys and studies, analyzing the functional and oncological outcome and quality of life of the patients after application of this surgical technique. I have reported in my thesis that laser cordectomy has many advantages over conventional modes of treatment of early vocal cord cancers. The perioperative morbidity and complications are negligible, the period of hospitalization is brief, and tracheotomy which has a negative impact on the postoperative quality of life, is not required. Deglutition is not disturbed, while partial laryngectomies frequently lead to varying degrees of prolonged aspiration. In local recurrences, the re-treatment options are better after initial laser surgery as compared with primary radiotherapy or open surgery, since wound complications as a result of previous irradiation are not encountered and the laryngeal framework is still intact, preventing the early extralaryngeal spread of local recurrences. Therefore, such recurrences allow further organ-sparing procedures, and "final salvage" treatment such as radiotherapy or total laryngectomy is seldom required. Special attention should be drawn to the importance of a long and careful follow-up, since the incidence of second primary tumors is relatively high and new tumors may occur any time after the initial diagnosis. Our long-term oncologic results demonstrate that we achieved results with laser surgery as concerns the rates of local or locoregional tumor control, overall and tumor-specific survival or larynx preservation that were similar to or

better than the rates of radiotherapy or open partial surgery. Our study has clearly revealed that laser cordectomy is no longer a treatment modality restricted to highly selected patients, but is a real alternative as primary treatment to radiotherapy or external partial laryngectomy for early carcinomas of the glottis.

In 1997, as a French governmental fellowship holder, I had the opportunity to spend 3 months in the Gustave-Roussy Institute, in Villejuif, which is one of the largest oncological centers in the world. I established a very good scientific relationship with the chief of the Department of Otorhinolaryngology, Head and Neck Surgery, Professor Luboinski. In 2000, I spent a further 2-year postgraduate fellowship there in the "Clinical Research in Oncology" program. During this training I become familiar with the techniques of fluorescence videoendoscopy. After returning to Hungary, I introduced these new techniques into our clinical practice, supplementing the already known and used 5-ALA-induced protoporphyrin IX. fluorescence endoscopy. Although laryngomicroscopy is the standard method in the diagnosis and treatment of glottic precancerosis and early cancers, there is still a need for improvement of our preoperative assessment. Our results have shown that AF videoendoscopy enables laryngologist to distinguish between benign hyperplastic lesions and precancerous epithelium with a very high sensitivity rate. Better pictures can be obtained in cases of flat lesions, mostly on the surface of the true vocal cords. Furthermore, the demarcation of the lesions and dysplastic margins around tumors can be intensified by the color contrast. Using this enhanced delineation of the lesions, we have modified our surgical concept, and used AF videoendoscopy for intraoperative control of surgical margins after the endoscopic CO_2 laser resection of glottic cancer. We believe that this application of photodiagnosis as a complementary visual aid in the intraoperative control of the surgical margins was the first such use in Hungary. The detection of additional lesions on the mucosal surface, invisible on conventional white light endoscopy, clearly illustrates another possible use of this method, for the regular follow-up of treated cancerous patients, or in the routine screening of a high-risk population for precancerosis or tumorous lesions.

SUMMARY OF THE NEW FINDINGS

1. I constructed a larynx holder, which was the first device reported in the international literature. This model can be made from easy-to-find materials by anyone, there is no need for whole cadaveric preparations and special room for practicing with it. The existing temporal bone laboratory is convenient for this purpose. With the help of this fixator all kinds of endolaryngeal surgical techniques like laser surgery and even the translaryngeal suturing techniques can be practiced and learned. It has been tested and utilized in a local institution and in many advanced international laryngeal surgery courses, and perfectly fulfils the purposes for which it was designed (I, III, X).

2. We have demonstrated that the number of treated precancerosis, mainly those, which transformed to invasive cancer, is much lower, than the number of vocal cord cancers without any pathway of precancerosis. This difference represents a significant disproportion, which is inconsistent with the theory that premalignant lesions always precede invasive cancer of the vocal cords. In our opinion, carcinogenesis of the vocal cords presumably has different forms in regard of its duration and aggressiveness, and laryngomicroscopy with or without CO_2 laser, proved to be efficient to eliminate these lesions, and reduce the number of glottic cancers. (II, VII).

3. Our data proved that CO_2 laser surgery for early cancer of the vocal cords is a minimally invasive technique; it has minimal postoperative complications, and postoperative morbidity. It gives good functional and anatomical results, has positive effects on quality of life of patients. The oncological results are better than or equal to other treatment options. We believe that laser cordectomy is a real alternative to radiotherapy or open surgery and it should be the first choice of treatment for early vocal cord carcinoma (IV, VIII, IX, XII, XIII).

4. I have demonstrated that autofluorescence videoendoscopy is a simple and clinically feasible new endoscopic method for early detection of premalignant and early malignant vocal cord lesions. With its use, the delineation of healthy and affected mucosa is possible, precancerosis and tumorous lesions can be visualized and differentiated from healthy mucosa. There is no need for external photosensibilisant; it provides a safer intraoperative control of surgical margins after laser surgery. It seems to be a reliable method to discover subclinical, invisible lesions and it can be extended for the follow-up, selection or screening of the group of high risk patients (V, VI, XI, XIV).

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Chapter 4

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