Epidemiology, Clinical Characteristics and Treatment Outcome of Laryngeal Cancer

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HANNU RAITIOLA

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University of Tampere
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ACADEMIC DISSERTATION
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ACADEMIC DISSERTATION

To be presented, with the permission of
the Faculty of Medicine of the University of Tampere,
for public discussion in the main auditorium of
Building K, Medical School of the University of Tampere,
Teiskontie 35, Tampere, on June 16th, 2000, at 12 o'clock.

University of Tampere
Tampere 2000

To my family

CONTENTS

ABSTRACT

Epidemiological factors, clinical characteristics, treatment and prognosis of laryngeal cancer were evaluated among 318 patients diagnosed and treated at the Tampere University Hospital during a 30-year period between 1962 and 1991. There were 302 (95%) male and 16 (5%) female patients with a median age of 62.8 years. In 312 (98%) patients the histological finding was squamous cell carcinoma.

During the study period the age-adjusted annual incidence in males decreased from the highest 5-year average of 6.7/100,000 in 1967-1971 to 2.6/100,000 in 1987-1991. The female incidence remained unchanged in 0.2/100,000/year. The most prominent incidence decrease occurred among males aged 40-49 years. From the first to the last 10-year period the proportion of supraglottic tumours decreased from 2/3 to 1/3.

In both sexes the proportion of smokers was significantly higher among patients with laryngeal cancer than in the population. Low socio-economic status was also significantly associated with increased risk of laryngeal cancer. Favourable changes in the smoking habits of Finnish men seem to be the most important contributor to the declining occurrence.

The proportion of early stage lesions was higher among glottic tumours and patients with a supraglottic tumour presented more often with neck node metastases. Hoarseness was the most common symptom, being more frequent in glottic than in supraglottic cases. Other symptoms like sore throat, globus and dysphagia were more often associated with supraglottic lesions.

The 5-year disease-specific survival of patients with a glottic and supraglottic tumour was 81% and 71%, respectively. This difference was not statistically significant. Also when analysed by T-category, location of the tumour did not affect the survival significantly. Higher T-category and presence of neck node metastases were the most important predictors of poorer prognosis.

Most early glottic carcinomas were treated with primary radiotherapy. Among the 60 patients with a glottic T1 and the 12 with a glottic T2 tumour treated by megavoltage irradiation since 1970, a higher number of involved vocal cord thirds indicated poorer primary locoregional control in multivariate analysis. Extension of the tumour to the posterior vocal cord third and higher T-category predicted poorer disease-specific survival.

ABBREVIATIONS

c	clinical
CI	confidence interval
CT	computed tomography
EGFR	epidermal growth factor receptor
FNAC	fine needle aspiration cytology
Gy	Gray
HR	hazard rate
Ki-67	cell proliferation-associated human nuclear antigen
LSCC	laryngeal squamous cell carcinoma
MIB-1	antibody for Ki-67
MRI	magnetic resonance imaging
n	number of cases
p	pathological
p53	tumour suppressor gene p53 protein
PAH	polycyclic aromatic hydrocarbons
PCNA	proliferating cell nuclear antigen
PET	positron emission tomography
RND	radical neck dissection
SCC	squamous cell carcinoma
TNM	tumour-node-metastasis classification system
UICC	Union Internationale Contre le Cancer (International Union Against Cancer)
US	ultrasound

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, referred to in the text by their Roman numerals. In addition, previously unpublished results are presented.

I Raitiola H and Pukander J (1997): Changing trends in the incidence of laryngeal cancer. Acta Oncol 36:33-36.

II Raitiola H and Pukander J (1997): Etiological factors of laryngeal cancer. Acta Otolaryngol Suppl (Stockh) 529:215-217.

III Raitiola H, Pukander J and Laippala P (1999): Glottic and supraglottic laryngeal carcinoma: differences in epidemiology, clinical characteristics and prognosis. Acta Otolaryngol (Stockh) 119:847-851.

IV Raitiola H and Pukander J: Symptoms of laryngeal carcinoma and their prognostic significance. Acta Oncol, in press.

V Raitiola H, Wigren T, Pukander J (2000): Radiotherapy outcome and prognostic factors in early glottic carcinoma. Auris Nasus Larynx 27:153-159.

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INTRODUCTION

Laryngeal cancer is the most common non-cutaneous head and neck malignancy. In Finland it accounts nowadays for about 1.1% of all new cancers in males and 0.1% in females. The current annual age-adjusted incidence is about 3/100,000 in men and 0.3/100,000 in women (Finnish Cancer Registry 1997). The incidence rates vary widely, but a marked predominance of men is a world-wide observation. Rising incidence trends in both sexes have been reported from several countries (Ayiomamitis 1989, DeRienzo et al. 1991, Robin et al. 1991, Engeland et al. 1993, Capocaccia et al. 1994). Tobacco smoking and high consumption of alcohol are generally regarded as the major risk factors for laryngeal cancer (IARC 1986, IARC 1988). Some environmental, occupational and dietary factors may also play a role in laryngeal carcinogenesis. Over 90% of laryngeal malignancies are squamous cell carcinomas.

For classification purposes the larynx is divided into three anatomical regions: the supraglottis, the glottis and the subglottis. Subglottic tumours are rare, comprising only a few per cent of all laryngeal malignancies. The glottic to supraglottic location ratio varies in different reports, but generally glottic carcinoma is more common (Kleinsasser 1988, Marck and Lupin 1989, Robin et al. 1991, Stephenson et al. 1991, Tuyns 1994). Supraglottic cancer has been found more prevalent in some Mediterranean and Latin American areas (De Stéfani et al. 1985, Tuyns et al. 1988, Basut et al. 1996), and previously also in Finland. Already in 1944 attention was drawn to the high proportion of supraglottic tumours among Finnish patients (Mustakallio 1944) and this finding was confirmed in the 1960s (Lauerma 1967, Taskinen 1969).

In the 1960s the occurrence of laryngeal cancer was over three times higher in Finland than in the other Nordic countries (Mårtensson 1975, Engeland et al. 1993). The statistics of the Finnish Cancer Registry show that the incidence has decreased strikingly since the early 1970s, but when the present study began there was no accurate data available of the current site distribution in Finland. Therefore it was decided to study the changes in the epidemiology of laryngeal cancer with special reference to alteration of site distribution inside the larynx. In addition, clinical behaviour, treatment and prognosis of the disease were evaluated.

REVIEW OF THE LITERATURE

Epidemiology

Incidence

Carcinoma of the larynx accounts world-wide for about 1.7% of all new cancer diagnoses (Parkin et al. 1999). While its incidence shows wide geographical variation, marked male dominance is a universal finding. In France, Italy, Poland and Spain, age-adjusted incidences as high as 15-18 cases per 100,000 men per year have been registered while the lowest male incidence of 0.7/100,000 has been reported from Qidong city, China (Parkin et al. 1997). In females the figures vary between 0.1/100,000 and 2.9/100,000 (Parkin et al. 1997). The age-adjusted global incidence estimate for the year 1990 is 5.7/100,000 person-years in men and 0.7 in women (Parkin et al. 1999). Rising incidence trends have been reported from several areas and mostly in both sexes (Ayiomamitis 1989, Guénel et al. 1990, DeRienzo et al. 1991, Robin et al. 1991, Engeland et al. 1993, Capocaccia et al. 1994, Tuyns 1994, Cattaruzza et al. 1996).

In Finland the male age-adjusted annual incidence of laryngeal cancer has decreased exceptionally from the highest five-year average figure of 7.2/100,000 in 1967-71 to 3.1/100,000 in 1991-95. The female incidence has remained practically unchanged, being about 0.3/100,000. The average annual number of new laryngeal cancer cases was 120 in 1991-95 (Finnish Cancer Registry 1989-1997).

Age and sex

Laryngeal cancer is mainly a disease of middle-aged and elderly men, with peak incidence in the sixth to eighth decades of life (Rothman et al. 1980, Kleinsasser 1988, Guénel et al. 1990, Robin et al. 1991). Women are often found to be affected earlier in life than men and the proportion of women is higher in younger age-groups (Lauerma 1967, Rothman et al. 1980, Kleinsasser 1988, Robin et al. 1991, Stephenson et al. 1991). The overall male to female ratio varies between 4:1 and 20:1 (Yang et al. 1989, Stephenson et al. 1991, Silvestri et al. 1992, Parkin et al. 1997),

with an increasing proportion of women as a common finding (Kleinsasser 1988, Ayiomamitis 1989, DeRienzo et al. 1991, Robin et al. 1991, Harris et al. 1993, Cattaruzza et al. 1996).

Location inside the larynx

For classification of tumours the larynx is divided into three anatomical regions: the supraglottis, the glottis and the subglottis. Subglottic tumours are rare, comprising only a few per cent of laryngeal malignancies. The frequency of glottic tumours compared with supraglottic lesions varies in different parts of the world. Glottic location generally dominates over the supraglottis, the glottic to supraglottic ratio being usually about 2:1 (Mårtensson 1975, Kleinsasser 1988, Marck and Lupin 1989, Yang et al. 1989, Robin et al. 1991, Stephenson et al. 1991, Tuyns 1994). Supraglottic cancer has been found more prevalent in certain regions of France (Brugère et al. 1986, Guénel et al. 1988, Tuyns et al. 1988), Italy (Tuyns et al. 1988, Merletti et al. 1990, Silvestri et al. 1992), Spain (Tuyns et al. 1988), Turkey (Basut et al. 1996, Kurtulmaz et al. 1997) and Uruguay (De Stéfani et al. 1985, De Stéfani et al. 1987).

According to reports based on patients treated at the Helsinki University Central Hospital in 1936-61, two thirds of laryngeal cancers were supraglottic (Lauerma 1967, Taskinen 1969). On the other hand, in reports from the Turku University Central Hospital from the periods 1955-71 (Nordman and Kyttä 1978) and 1981-90 (Grénman et al. 1996) 60% of the tumours were glottic. According to a recent report including data from the five university hospitals of Finland, 50-68% of laryngeal cancers were glottic in the late 1980s and 1990s (Mäkitie et al. 1999). Thus, the glottic to supraglottic incidence ratio seems to have altered considerably in Finland. Unfortunately comprehensive information about the site distribution for the whole country is not available because the Finnish Cancer Registry has not systematically recorded the anatomical site of laryngeal tumours.

Higher relative frequency of supraglottic tumours among women is a usual finding (Wynder et al. 1976, Marck and Lupin 1989, Yang et al. 1989, Robin et al. 1991, Stephenson et al. 1991, Silvestri et al. 1992, Harris et al. 1993, Grénman et al. 1996), and in some studies supraglottic lesions have been more common in younger patients (Lauerma 1967, Stephenson et al. 1991, León et al. 1998).

Risk factors

Smoking

Tobacco smoking has been established as the main risk factor for laryngeal cancer (IARC 1986). A vast majority (88-98%) of the patients with laryngeal carcinoma are smokers (Kleinsasser 1988). The carcinogenic effect of tobacco smoke is correlated with the intensity and duration of smoking (Wynder et al. 1976, Tuyns et al. 1988, Muscat and Wynder 1992, Zheng et al. 1992). Air-cured "black" tobacco seems to be more carcinogenic than "blond", flue-cured tobacco (De Stéfani et al. 1987, Tuyns et al. 1988). The risk of laryngeal cancer has been found higher among smokers of hand-rolled than factory-made cigarettes (De Stéfani et al. 1992) and non-filtered cigarettes are more harmful than filter cigarettes (Wynder et al. 1976, Tuyns et al. 1988).

Alcohol drinking

The relationship between the occurrence of laryngeal cancer and alcohol consumption has been consistently demonstrated by several epidemiological studies (Wynder et al. 1956, Wynder et al. 1976, IARC 1988, Kleinsasser 1988, Tuyns et al. 1988). Alcohol seems to be more significant in the etiology of supraglottic than glottic cancer, and its carcinogenic effect is also dose-dependent (Wynder et al. 1976, Tuyns et al. 1988, Muscat and Wynder 1992). There is no evidence that the effect is dependent on the type of alcoholic beverage (IARC 1988). Most studies have concluded that the joint effect of alcohol and tobacco is multiplicative (Guénel et al. 1988, Tuyns et al. 1988, Zatonski et al. 1991, Maier et al. 1992a).

Other risk factors

Dietary factors such as low fruit and vegetable intake (De Stéfani et al. 1987, Zheng et al. 1992, Estève et al. 1996), poor nutrition in general (Zatonski et al. 1991) and consumption of salted meat and fish (Zheng et al. 1992, De Stéfani et al. 1995) have been associated with elevated laryngeal cancer risk. The available evidence indicates that occupational

exposure to asbestos increases the risk of laryngeal malignancy (Smith et al. 1990, Muscat and Wynder 1992, Gustavsson et al. 1998). Other possible occupational risk factors include diesel exhaust (Muscat and Wynder 1992), wood (Maier et al. 1992b, Muscat and Wynder 1992, Pollán and López-Abente 1995), rubber (Muscat and Wynder 1992), cement (Maier et al. 1992b) and coal (Zheng et al. 1992) dusts and sulphuric acid mists (Steenland 1997). Human papillomavirus (HPV) infection (Syrjänen et al. 1987, Mineta et al. 1998) and gastroesophageal reflux (Morrison 1988, Ward and Hanson 1988, Freije et al. 1996) have also been proposed to affect laryngeal carcinogenesis. Their role has, however, not yet been established (Sugár et al. 1996, Chen et al. 1998).

Smoking and alcohol consumption in Finland

Cigarette smoking was introduced to Finland from Russia in the middle of the nineteenth century. The industrial manufacturing of cigarettes started in Finland already in 1859 and by the beginning of the 1880s the annual production had reached 100 million. By 1901 the number had risen to nearly 500 million and cigarette smoking had become general throughout the country (Pernu 1960). People of the other Nordic countries favoured other forms of tobacco and smoking of cigarettes became popular much later than in Finland (Pedersen et al. 1969, Beese 1972). Up to the 1960s, consumption of factory-made cigarettes was significantly higher in Finland but the proportion of smokers has been lower than in the other Nordic countries (Beese 1972, Rimpelä 1978). Heavy smoking has thus been more common in Finland (Teppo 1984). Smoking among Finnish males has decreased gradually since the early 1960s. In 1960, 58% of Finnish males were daily smokers. In the early 1970s the figure was around 45% and in 1995 as low as 29% (Valtonen and Rimpelä 1984, Statistics Finland 1996). The female percentage of daily smokers has increased from 14 to 20 during the period of 1960-1995. In males born in the 1920s and before, the highest prevalence of smoking has been over 70% in the 1940s and 50s. Among males born in the 1930s and later, the proportion has been lower than in previous cohorts (Rimpelä 1978). Another important phenomenon was the gradual abandonment of the "pilli" and "pölli" cigarettes after the 1950s. These "Russian-style" cigarettes, with a high content of tar, accounted for about 45% of the cigarette consumption in Finland as late as 1956, after which modern filter cigarettes quickly replaced them (Beese 1972, Rimpelä 1978).

The registered consumption of alcoholic beverages in Finland was as low as 2-3 litres of 100% alcohol per inhabitant until the late 1960s, after which it has grown nearly threefold. This increase is largely due to the consumption of beer, but consumption of wine and spirits has also increased. (Engeland et al. 1993, Statistics Finland 1998)

Histology

Squamous cell carcinoma (SCC) is by far the most common histologic finding in laryngeal malignancy. It accounts for more than 90% of laryngeal cancers in most studies (Alexander and Cassady 1966, Marck and Lupin 1989, Sasaki and Carlson 1993, Krecicki et al. 1998). Carcinoma in situ and verrucous squamous cell carcinoma both account for a few per cent of laryngeal cancers (Ferlito 1976, McCaffrey et al. 1998).

Other rare malignancies may derive from all cell types present in the larynx. Epithelial tumours include lymphoepithelioma, melanoma and pseudosarcomatous carcinoma. Two major types of carcinoma of glandular origin are those that arise from neuroendocrine cells and those that arise from the minor salivary glands: adenocarcinoma and adenoid cystic, acinic cell, mucoepidermoid, adenosquamous and anaplastic carcinoma. Chondrosarcoma, fibrosarcoma and rhabdomyosarcoma are the most common malignancies arising from the structural elements of the larynx although other sarcomas have also been reported. Tumours arising from lymphoreticular tissue include lymphoma, plasmocytoma, mycosis fungoides and fibrous histiocytomas. (Sasaki and Carlson 1993)

TNM classification

The anatomical sites and subsites referred to in the TNM classification are listed in Table 1. Tables 2 and 3 present the 1987 UICC TNM classification (fourth edition, Hermanek and Sobin 1987) and stage grouping used in this study. The classification applies only to histologically confirmed carcinomas. Clinical classification (TNM or cTNM) is based on evidence acquired before treatment. Procedures for assessment of clinical T category of laryngeal carcinoma are physical examination, laryngoscopy and imaging. N and M categories are estimated by physical examination and imaging. Pathological classification (pTNM) is based on the pre-treatment evidence supplemented or modified by additional evidence acquired from surgery and from pathological examination.

Table 1. *Anatomical sites and subsites of the larynx according to the 1987 UICC TNM-classification (Hermanek and Sobin 1987)*

1. Supraglottis
   Epilarynx (including marginal zone)
   i) Suprahyoid epiglottis (including tip, lingual and laryngeal surfaces)
   ii) Aryepiglottic fold
   iii) Arytenoid
   Supraglottis excluding epilarynx
   iv) Infrahyoid epiglottis
   v) Ventricular bands (false cords)
   vi) Ventricular cavities

2. Glottis
   i) Vocal cords
   ii) Anterior commissure
   iii) Posterior commissure

3. Subglottis

Table 2. *TNM clinical classification of laryngeal carcinoma (Hermanek and Sobin 1987)*

T - Primary tumour

TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
Tis Carcinoma in situ

Supraglottis
T1 Tumour limited to one subsite of supraglottis with normal vocal cord mobility
T2 Tumour invades more than one subsite of supraglottis or glottis, with normal vocal cord mobility
T3 Tumour limited to larynx with vocal cord fixation and/or invades postcricoid area, medial wall of piriform sinus or pre-epiglottic tissues
T4 Tumour invades through thyroid cartilage and/or extends to other tissues beyond the larynx, e.g. to oropharynx, soft tissues of the neck

Glottis
T1 Tumour limited to vocal cord(s) (may involve anterior or posterior commissures) with normal mobility
- T1a Tumour limited to one vocal cord
- T1b Tumour involves both vocal cords

T2 Tumour extends to supraglottis an/or subglottis, and/or with impaired vocal cord mobility
T3 Tumour limited to the larynx with vocal cord fixation
T4 Tumour invades through thyroid cartilage and/or extends to other tissues beyond the larynx, e.g. to oropharynx, soft tissues of the neck

Subglottis
T1 Tumour limited to the subglottis
T2 Tumour extends to vocal cord(s) with normal or impaired mobility
T3 Tumour limited to the larynx with vocal cord fixation
T4 Tumour invades through cricoid or thyroid cartilage and/or extends to other tissues beyond the larynx, e.g. to oropharynx, soft tissues of the neck

N - Regional lymph nodes

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2 Metastasis in a single ipsilateral lymph node, more than 3 cm but no more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
- N2a Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
- N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
- N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension

N3 Metastasis in a lymph node more than 6 cm in greatest dimension

Note: Midline nodes are considered ipsilateral nodes.

Distant metastases

MX Presence of distant metastases cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

Table 3. *Stage grouping of laryngeal carcinoma (Hermanek and Sobin 1987)*

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IV	T4	N0, N1	M0
	Any T	N2, N3	M0
	Any T	Any N	M1

In the fifth edition of UICC TNM classification (Sobin and Wittekind 1997), some changes have been made to the T classification of supraglottic tumours, and stage IV is now divided into 3 substages: IVA, IVB and IVC (Iro and Waldfahrer 1998).

Clinical presentation

Symptoms of laryngeal cancer vary according to the location, size and degree of invasion of the tumour. Hoarseness is the cardinal symptom, which in glottic cases often occurs even with small tumours. Supraglottic and more advanced glottic lesions may cause miscellaneous symptoms like sore throat, globus sensation, dysphagia and dyspnoea, which is common also in subglottic cases. A neck mass of nodal metastasis or of direct extension of the tumour may also be present. The symptoms seem to appear later in supraglottic than in glottic disease. (Kaufman et al. 1980, Kleinsasser 1988, Merletti et al. 1990, Dolan et al. 1998)

Patients with a supraglottic tumour present more often with locally advanced disease and neck node metastases. Supraglottic tumours also tend to metastasize earlier than glottic ones. Distant metastases are

usually detected only in a few per cent of laryngeal cancer patients at the time of diagnosis. (Stell 1990b, Reid et al. 1991, Shah et al. 1997, Krecicki et al. 1998)

Diagnostic procedures

Endoscopy

Even though the idea of examining the larynx had been considered long before, singing teacher Manuel Garcia was the first to fully visualize the larynx (his own) with a mirror in 1854. After that, Ludwig Türck and Johann Czermack applied the technique to medical practice (Koltai and Nixon 1989). Indirect mirror laryngoscopy is the simplest method for detecting laryngeal tumours. In the majority of cases a careful and experienced examiner can recognize a carcinoma of the larynx and estimate its approximate extent by indirect laryngoscopy alone. In addition to mirror examination, rigid telescopes with an angled lens may be used to inspect the larynx. These instruments have the advantage that they magnify the image, permit photography or videotaping and can be coupled to a monitor for teaching purposes. Laryngoscopic technique using flexible fibre optics was first published in 1968 by Sawashima and Hirose and fibreoptic laryngoscopes were further developed in the 1970s (Williams et al. 1975, Silberman et al. 1976). Fibreoptic laryngoscopy is of great value in the assessment of patients who are difficult to examine by indirect laryngoscopy. It can also be employed in some situations where direct laryngoscopy is difficult or impossible (Brimacombe et al. 1996). (Tucker 1987, Kleinsasser 1988)

Although a biopsy of a laryngeal tumour can be taken under local anaesthesia by indirect laryngoscopy or by transnasal fiberoscopy (Goldman and Roffman 1975, Bastian et al. 1989), direct laryngoscopy is the main method for further evaluation and biopsy of laryngeal neoplasms (Pashcow and Mattucci 1983, Kleinsasser 1988). Direct laryngoscopy originates from 1895, when Kirstein visualized the endolarynx directly. The suspension laryngoscope was introduced by Killian in 1909 and improved by Lynch in 1915 (Pashcow and Mattucci 1983). Up to the 1960s, direct laryngoscopies were performed mostly under local anaesthesia (Calcaterra and House 1974). The use of a

binocular operating microscope for direct laryngoscopy was first reported in 1960 by Scalco et al., and during the 1960s microlaryngoscopy and endolaryngeal microsurgery were further developed (Kleinsasser 1968, Jako 1970). This progress was made possible by the development of general anaesthetic methods suitable for laryngoscopy (Priest and Wesolowski 1960, Kleinsasser 1968, Howard and Jako 1969). Evolution of various jet ventilation techniques after the early 1970s has improved the visualization of the larynx (Baer 1985, Hunsaker 1994). Microlaryngoscopy under general anaesthesia using a suspension laryngoscope is currently the standard method for evaluation and biopsy of laryngeal tumours. It allows accurate study of the surface and extent of the tumour, biopsies can be taken from accurately chosen sites, and small tumours can be excised completely. (Kleinsasser 1988)

Imaging of the larynx

Clinical examination and endoscopy provide the most important pre-treatment assessment of laryngeal cancer. Imaging of the larynx is indicated if the findings may affect classification and treatment of the laryngeal tumour. It is generally accepted that small glottic cancers (T1 and perhaps small T2 lesions) do not need imaging before therapy unless the anterior commissure is involved. The value of imaging of the larynx is also questionable if the only treatment to be considered is total laryngectomy. Conversely, accurate pre-treatment evaluation of tumour extent is particularly important if a partial laryngectomy is planned. (Kleinsasser 1988, Dullerud et al. 1992, Phelps 1992, Williams 1997, Castelijns et al. 1998)

Before the era of computed tomography (CT), the larynx was imaged by plain radiographs, xeroradiography, laryngography and linear tomography (Kleinsasser 1988). Their value in pre-treatment evaluation of laryngeal cancer was, however, limited (Williams 1997). At present, the cross-sectional imaging modalities CT and magnetic resonance imaging (MRI) have replaced these conventional radiologic methods. They provide more accurate information of deep invasion of the tumour, submucous spread and extension to the surrounding tissues—which can not be achieved by endoscopy (Kleinsasser 1988, Phelps 1992, Williams 1997, Castelijns et al. 1998).

The role of CT—the ruling method for more than a decade—is increasingly challenged by MRI. Many investigators consider MRI as the method of choice for imaging of the larynx (Giron et al. 1993, Becker

1998, Castelijns et al. 1998). If properly performed, both CT and MRI usually provide sufficient pre-treatment information about the extent of the disease, the involvement of critical anatomic structures and nodal metastases (Williams 1997). Close co-operation between the clinician and the radiologist is essential to use these diagnostic tools optimally (Williams 1997, Becker 1998). The major advantage of MRI is its ability to provide higher soft tissue contrast. CT, on the other hand, allows faster image acquisition and is less susceptible to artefacts (Becker 1998). Perhaps the most significant advantage of MRI is its higher sensitivity in detecting neoplastic cartilage invasion. However, the specificity of MRI is limited because non-neoplastic inflammatory changes in the cartilages may simulate cartilage invasion (Becker et al. 1995). Positron emission tomography (PET) has given promising results in differentiating recurrent tumour from postirradiation tissue sequelae (McGuirt et al. 1995, Greven et al. 1997).

Evaluation of the neck

Cervical lymph node metastases play an essential role in the treatment planning and prognosis of patients with laryngeal carcinoma. Palpation is the primary method to evaluate the neck node status. However, staging of the neck by palpation only in patients with head and neck carcinoma is known to be inaccurate due to common false-negative and false-positive findings (Friedman et al. 1990, Shah 1990, Kowalski et al. 1995).

CT, MRI and ultrasound (US) are superior to palpation in detecting metastatic cervical lymph nodes (van den Brekel et al. 1993, Atula et al. 1997, Takashima et al. 1997). The specificity of these methods is, however, not high enough to reliably exclude metastasis in nodes falsely positive by palpation (van den Brekel et al. 1993). When US is combined with fine needle aspiration cytology (FNAC), the specificity increases to 93-100% (Baatenburg de Jong et al. 1989, van den Brekel et al. 1993, Takashima et al. 1997). In the study of van den Brekel et al. (1993), based on neck dissection specimens, US-guided FNAC was more accurate than CT and MRI for staging both clinically negative and positive necks. Thus, US-guided FNAC seems to be the most reliable technique for detecting or excluding the presence of neck node metastases preoperatively. However, if the primary laryngeal tumour needs CT or MRI examination, these modalities are often sufficient also for the evaluation of the neck (van den Brekel et al. 1993). PET may also

be a useful diagnostic aid in detecting cervical lymph node metastases (Adams et al. 1998, Myers et al. 1998).

Treatment

Laryngeal cancer can be treated by radical radiotherapy, by surgery or by a combination of these modalities. Chemotherapy has previously played a minor adjuvant or palliative role in the treatment of advanced tumours, but its importance is increasing and it has even been proposed to be combined in the treatment of early stage disease (Laccourreye et al. 1999a, Laccourreye et al. 1999b). In many patients with an early stage (I or II) tumour, the disease can be cured with single-modality therapy consisting of radiotherapy or surgery. Advanced-stage carcinomas, in contrast, often require multimodality treatment. (Shah et al. 1997)

Several factors have to be considered in the planning of the treatment. These include the age and general condition of the patient, his personal preferences and social circumstances, the treatment facilities available and, above all, the location and stage of the tumour. The intent of the treatment is primarily to eradicate the tumour and secondly to preserve the function of the larynx as well as possible. Some patients are willing to sacrifice a portion of the probability of cure in choosing a less radical treatment that results in better function (Hoffman et al. 1997).

Surgery of the larynx

Many different techniques for surgical treatment of laryngeal cancer have been devised since Buck in 1851 first performed a successful partial laryngectomy through laryngofissure (Alberti 1975), and Billroth carried out the first total laryngectomy for cancer in 1873 (Stell 1975). Until the beginning of the twentieth century, serious complications were very common and operative mortality was high in laryngeal cancer surgery. The morbidity and mortality, however, decreased as experience increased. In 1912, Gluck reported 160 total laryngectomies with no mortality in the last 62 cases . Partial laryngeal surgery was developed, among others, by Alonso (1947) and Ogura (Ogura 1958, Ogura et al. 1975), who popularized supraglottic laryngectomy. In the latter half of the twentieth century, conservation surgery of the larynx reached its culmination with the description of the near-total laryngectomy by Pearson (1981) and the supracricoid partial laryngectomy by Laccourreye et al. (1990a, 1990b).

Another approach to conservation surgery of the larynx is endoscopic procedures, which were first described in the end of the nineteenth

century and later by Lynch in 1920 (Kleinsasser 1988). However, precise endoscopic tumour resection only became possible with the development of endolaryngeal microsurgery. Good results of endoscopic surgery using nonlaser techniques have been reported in early glottic carcinoma (Lillie and DeSanto 1973, Kleinsasser 1988).

Endolaryngeal laser excision of carcinoma in situ and early T1 glottic carcinoma was introduced in the early 1970s (Strong and Jako 1972, Strong et al. 1973) and it is commonly used today in the treatment of glottic T1 and T2 carcinoma (Davis et al. 1990, Davis 1997, Remacle et al. 1997, Eckel et al. 1998). Also supraglottic tumours, even T3 and T4 lesions, have been treated successfully by transoral laser surgery (Steiner 1993, Zeitels 1997, Eckel et al. 1998, Iro et al. 1998).

In addition to esophageal speech and various external tone generators (artificial larynges), several surgical methods have been developed for the production of voice after total laryngectomy (Kleinsasser 1988). The tracheoesophageal puncture method first developed by Singer and Blom in 1978 (Singer and Blom 1980) is currently the surgical method of choice for vocal restoration (Blalock 1997). In this approach, a small valved silicone prosthesis is inserted into a surgically created tracheoesophageal fistula. The patient can then direct the expiratory airflow into the pharynx thereby creating vibratory activity for voice production. Several models of prostheses have later been introduced (Panje 1981, van den Hoogen et al. 1996, Hilgers et al. 1997).

Surgery of the neck

The classic technique of *en bloc* removal of the cervical lymphatics—radical neck dissection (RND)—was described by Crile in 1906 (Martin et al. 1951). RND is the standard procedure for removing all levels of cervical nodes, including the sternocleidomastoid muscle, the internal jugular vein and the accessory nerve. The modified radical neck dissection preserves one or more non-lymphatic structures. In the selective neck dissection, there is preservation of one or more lymph node groups routinely removed in the RND. Four subtypes of selective neck dissection are supraomohyoid, posterolateral, lateral and anterior neck dissection. (Robbins et al. 1991)

If the laryngeal tumour is treated surgically, the management of the clinically positive neck is usually also surgical. In general, a frequency of occult metastases exceeding 15-20% is considered to justify elective treatment of a clinically negative neck (Snow et al. 1992). On this basis,

supraglottic and T3-4 glottic cancers qualify for elective treatment. It is generally accepted that elective irradiation of the neck is as effective as elective neck dissection (Snow et al. 1992, Schuller and Bier-Laning 1997).

Radiotherapy and combined treatment

Surgery remained the mainstay of treatment of laryngeal cancer until the 1920s, when Coutard advocated fractionated external beam radiotherapy as a definitive treatment modality (Coutard 1932). Since the mid 1950s, cobalt-60 units and 2MeV generators and, later, linear accelerators have been used. With those modalities, high doses could be given to the tumours without moist desquamation of the skin, the major dose-limiting factor until then. By the mid-1960s, large series of patients had been treated and analysed and the treatment regimens had become established. Primary radiotherapy has been used especially in the treatment of early stage lesions, particularly T1-2 glottic tumours, surgery being reserved for the failures. Since the 1960s, planned combined surgery and irradiation for advanced stages has been widely used. (Fletcher 1986)

The conventional treatment of patients with advanced (stage III-IV) laryngeal cancer consists of total laryngectomy combined with radiotherapy. Because laryngectomy results in substantial functional handicaps, including the loss of natural voice, alterations in deglutition and breathing through a permanent tracheostoma, alternative forms of treatment have been developed (Anonymous 1991, Hoffman et al. 1997). Multimodality therapy including neoadjuvant chemotherapy and irradiation with surgical salvage has given encouraging results in preservation of the larynx without sacrificing survival (Lefebvre et al. 1996, Forastiere 1998, Lefebvre 1998). However, a recent larynx preservation meta-analysis showed a non-significant negative effect of chemotherapy used to avoid surgery (Pignon et al. 2000). This was considered to indicate that larynx preservation should remain investigational.

Current concepts of treatment modalities

Controversy regarding the best treatment of laryngeal carcinoma still exists due to the lack of prospective randomized comparisons of different treatment modalities (O'Sullivan et al. 1994, DiNardo et al. 1999).

Surgical alternatives extend from endoscopic excision to total laryngopharyngectomy. Radiotherapy options are multiplied by protocols differing in dose, extent and fractionation (Hoffman et al. 1997). Primary treatment of stage I-II disease often consists of surgery or radiotherapy as single modality (Shah et al. 1997, DiNardo et al. 1999). Surgical alternatives include endoscopic (laser) surgery and external "conservation" laryngeal procedures (Davis 1997, Osguthorpe and Putney 1997, Zeitels 1997). Advanced tumours may be treated with surgery alone, with combinations of surgery and radiation or with radical radiotherapy and surgical salvage (O'Sullivan et al. 1994, Shah et al. 1997). The value of induction and concomitant chemotherapy in laryngeal preservation protocols remains controversial. The currently accepted role of chemotherapy outside of research protocols is for palliation of incurable laryngeal cancers (Hoffman et al. 1997).

Prognosis

In Denmark, Norway and Sweden, the age-adjusted 5-year relative survival of males with laryngeal cancer has been at the level of 60-65% since 1960. Finland had lower relative survival (about 50%) in the 1960s, but the rate is now similar to that of the other Nordic countries (Engeland et al. 1995). According to a European study including data from 30 cancer registries in 11 countries from the period 1978-1985, the overall 5-year relative survival was 57% (Berrino et al. 1995). In a recently published study from the USA including 7188 patients with laryngeal squamous cell carcinoma diagnosed in 1980-1985, the overall 5-year disease-specific survival was 75% (Shah et al. 1997). When broken down by combined stage, the survival declined from 91% for stage I cases to 42% for stage IV cases. The best treatment results have been achieved in glottic T1 disease, where the initial and ultimate local control rates are 80% to 95% and 95 to 100%, respectively (Moose and Greven 1997). In addition to the extent of the disease, several factors related to patient or tumour may affect the prognosis.

Patient factors

Increasing age of the patient has been connected with poorer prognosis in some studies (Huygen et al. 1980, Pera et al. 1986). It seems, however, that the effect of age is mostly due to other factors than direct effect of age on the biological behaviour of the tumour (Stell 1990a). The prognosis of female patients has sometimes been observed to be better than that of males (Eiband et al. 1989, Kowalski et al. 1991, Boffetta et al. 1997). Poor general condition impairs survival by rendering many patients unsuitable for treatment, but it may also have a direct biological effect on tumour behaviour (Stell 1990a).

In a population-based study from northern Italy, heavy tobacco smoking worsened the prognosis in a dose-dependent manner (Crosignani et al. 1996). No effect was apparent for alcohol. The consumption of vegetables, citrus fruits, olive oil and orange juice was associated with better prognosis. An opposite association was found with butter and milk. In another Italian study, low socio-economic status and heavy smoking predicted poorer survival while diet and alcohol drinking did not affect the prognosis (Boffetta et al. 1997). On the other hand, in an earlier study alcohol drinking had an unfavourable prognostic effect, whereas smoking did not affect the survival (Pradier et al. 1993).

Tumour factors

Glottic carcinoma is generally considered to have a better prognosis than supraglottic disease. This seems, however, to be largely due to the more advanced stage and higher metastasizing potential of supraglottic tumours (Stell 1990b, Shah et al. 1997). The survival of laryngeal cancer declines along with the advancing of the T-category which has also been an independent prognostic factor in multivariate analyses (Pera et al. 1986, Gavilán et al. 1987, Kowalski et al. 1991). In addition to T-category, several other variables like tumour volume (Lo et al. 1998, Mukherji et al. 1999) and vocal cord mobility (Pradier et al. 1993) reflecting the extent of the primary tumour have been proposed to affect the prognosis. Ulceration of the tumour has also been a significant adverse prognostic factor in several studies (Pera et al. 1986, Eiband et al. 1989, Barra et al. 1990).

Presence of neck node metastases is a strong predictor of poor survival, and nodal status seems to be one of the best prognostic indicators in patients with laryngeal cancer (Stell 1990b, Reid et al. 1991, Pradier et al. 1993, Cappellari 1997). Extracapsular spread of nodal metastases is also an unfavourable prognostic factor, significantly

associated with tumour recurrence and decreased survival (Hirabayashi et al. 1991, Barona de Guzmán et al. 1993, Cappellari 1997). The number and location of involved nodes may affect the prognosis but the evidence is more contradictory (Cappellari 1997).

Lower differentiation of laryngeal squamous cell carcinoma has often been identified as a significant predictor of nodal metastases, recurrence and poor survival (Pera et al. 1986, Hirabayashi et al. 1991, Kowalski et al. 1991). On the other hand, many studies have failed to demonstrate the significant independent effect of tumour grade (Eiband et al. 1989, Manni et al. 1992, Pradier et al. 1993). The real prognostic value of histologic grade in LSCC appears to be limited due to the lack of a universally accepted grading system, the subjectivity and modest reproducibility of grading and the potential heterogeneity of grade within a particular tumour (Cappellari 1997).

There are considerable differences in the treatment outcome of laryngeal cancer that can not be explained by tumour stage or by conventional morphologic evaluation. Therefore, the potential role of novel biomarkers in predicting patient outcome and guiding treatment of laryngeal carcinoma has received increasing attention. These include DNA-ploidy, cell adhesion molecules, proliferation markers like PCNA and Ki-67 (MIB-1) and oncogenes like EGFR (c-erb B) and p53 (Devaney et al. 1997, Hirvikoski 1999). The role of these techniques in predicting tumour biology and therapeutic response remains uncertain (Cappellari 1997).

Second primary tumours

Second malignant neoplasia of the aerodigestive tract are common in patients with head and neck cancer. Slaughter et al. (1953) proposed the “field cancerization” hypothesis to explain the origin of these multiple tumours. This hypothesis proposes that long-term carcinogenic exposure results in “condemned mucosa”, from which multifocal tumours arise.

Up to 17% of patients with early glottic cancer have been found to develop a second malignancy of the upper aerodigestive tract or lung (Fujita et al. 1998, Narayana et al. 1998). The second primaries are also an important cause of death among these patients in whom the prognosis of the laryngeal cancer is good. Aggressive screening for second malignancies may have an essential role in improving survival of this patient group (Fujita et al. 1998).

PURPOSE OF THE STUDY

The present study was undertaken to evaluate epidemiological factors, clinical behaviour, treatment and prognosis of laryngeal cancer.

Special attention was given to:

1. Alterations in the occurrence of laryngeal cancer and location of the tumours inside the larynx during the study period of 1962-1991
2. Etiological factors and their impact on the incidence and site distribution
3. Comparison of epidemiological aspects, clinical behaviour and prognosis between glottic and supraglottic carcinoma
4. Symptoms and their prognostic value
5. Clinical features, treatment outcome and prognostic factors in early glottic carcinoma treated with primary radiotherapy

PATIENTS AND METHODS

Patients

The objective of the data collection was to review the records of all patients with laryngeal carcinoma diagnosed in the Tampere University Hospital area (Pirkanmaa Hospital District) during a period of 30 years, from 1962 to 1991. The basic data was generated from the hospital files, and then supplemented by data recorded in the Finnish Cancer Registry. During the study period, altogether 318 patients with a primary invasive laryngeal carcinoma were diagnosed. In addition, 13 cases of carcinoma in situ were found. These patients were not included in this study. Case histories of 309 patients were available in the hospital archives and all of them were also reported to the Cancer Registry. Information of nine cases diagnosed during the 1960s was available only in the Cancer Registry. These patients were either treated elsewhere or the records had been deleted from the hospital files.

In all patients with records available in the hospital files, the diagnosis was confirmed by histological examination. The histological finding was squamous cell carcinoma in 312 cases. Only these patients were included in the analyses of the clinical characteristics, treatment and prognosis (III, IV, V). Tumour site inside the larynx and the extent of the tumour were not known in the nine patients with only Cancer Registry data available. They were excluded from the respective analyses. In addition, 30 patients (15 supraglottic, 13 glottic and 2 subglottic) were excluded from the survival analyses, 5 due to insufficient follow-up data and 25 because their potentially curative primary or salvage treatment was abandoned for other than cancer-related reasons, e.g. patient refusal or other diseases. Because of the small number of subglottic cases, most analyses by tumour site were not performed among them. The tumours were reclassified according to the 1987 UICC TNM classification (Tables 1-3, Hermanek and Sobin 1987) on the basis of the initial clinical description and staging investigations. All patients were followed up for at least 5 years or until death, the median follow-up time being 5.6 years.

Reference data

The reference population data was derived from the official annual files of the Central Statistical Office of Finland and incidence figures for the whole country from the database of the Finnish Cancer Registry. Smoking habits of the population were drawn from the Tobacco statistics published annually by the Central Statistical Office of Finland (Statistics Finland 1996) and from earlier population-based studies (Valtonen and Rimpelä 1984).

Data analysis

The patient data was transferred directly from the patient records into an IBM-compatible PC using Microsoft Excel software. The statistical analyses were carried out by SPSS for Windows releases 5.0.1 and 6.1.

For annual incidence estimations, the denominator was the population at the end of each year. In incidence rates for periods of several years, the mean population of the corresponding period was used. To allow for the change in the age distribution of the population during the study period and to enable adequate comparisons with other studies, the incidence rates were adjusted for age according to the world standard population (Doll et al. 1966) by the direct method. To smooth out the reasonably heavy annual fluctuation, moving average incidences were used in some time trend figures. Spearman's rank correlation coefficient was applied to verify incidence trends over time.

The differences in means were analysed by the t-test, where Levene's test was applied to test the equality of variances. In groups with skewed distributions, the Mann-Whitney *U* test and Kruskall-Wallis analysis of variance were employed. Differences in proportions were analysed by means of the χ^2-test and Fisher's exact test. A p-value less than 0.05 was considered as statistically significant.

Symptom duration was calculated from the beginning of the earliest symptom reported by the patient to the date of the diagnostic biopsy; the length of each symptom was also recorded separately. The survival patterns were estimated by the Kaplan-Meier method, and the log-rank test was applied to compare the survival functions. Survival times were calculated from the beginning of therapy to the first histologically verified recurrence for primary locoregional control and to the date of

death for disease-specific survival. Patients living without known recurrence and those who died of intercurrent diseases were censored at the last follow-up or at the date of death, respectively. For disease-specific survival, all tumour- and treatment-related causes of death were considered. Prognostic factors were evaluated using Cox proportional hazard modelling. In multivariable analyses, the variable selection was based on a stepwise procedure where a variable was entered into the model at a significance level of 0.05 or less and removed at a level of 0.1 or more, which are the usual default values.

Ethics

The study was carried out according to the approval of the Ethics Committee of Tampere University Hospital. Permission to obtain patient data from the Finnish Cancer Registry was granted by the Finnish Ministry of Social Affairs and Health. Because of the retrospective nature of this study, the patients or their relatives were not contacted.

RESULTS

Patient and tumour characteristics (I)

There were 302 (95%) male and 16 (5%) female patients. The median age of men at the time of diagnosis was 62.8 (range 20-87) years and that of women 63.0 (20-78) years. Only one male and one female patient were younger than 35 years (both 20 years).

In 312 (98%) patients the histological finding was squamous cell carcinoma. Four verrucous carcinomas, one pseudosarcomatous and one adenosquamous carcinoma were found. Of the 180 (57%) SCC:s with the histological grade available, 85 (47%) were well, 65 (36%) moderately and 30 (16%) poorly differentiated.

Of the 309 evaluable patients, 129 (42%) had a supraglottic, 170 (55%) a glottic and 10 (3%) a subglottic tumour. There was no significant difference in the sex distribution (percentage of females 4.7 vs. 5.9) or median age (62.4 vs. 63.4 years) between the supraglottic and glottic cases. All subglottic tumour patients were men with a median age of 60.6 years.

Incidence (I)

During the study period, the average population of the Tampere University Hospital area was about 400,000. The annual number of new cases of laryngeal carcinoma varied between 4 and 25 (mean 10.6). In males, the annual age-adjusted incidence ranged from 1.9/100,000 to 11.3/100,000, the mean value being 4.4/100,000. The rate of females was between 0 and 0.9, mean 0.2. Although the male incidence showed a marked fluctuation, there was a significant ($p=0.001$) decrease over the study period. The highest 5-year average incidence was 6.7 (95% CI 5.2-8.3) in 1967-71 and the lowest was 2.6 (95% CI 1.7-3.4) in 1987-1991 (I, Fig. 1). In females, the incidence rates showed no distinct trend. However, due to the decrease of occurrence in men, the male to female incidence ratio decreased from 38:1 in 1962-71 to 18:1 in 1982-91.

The occurrence increased with age in both sexes and the age-specific incidence was higher among males than females in all age groups older

than 35 years. The peak incidence was in the age group 65-69 years in males and 75-79 years in females (I, Fig. 2). The most prominent incidence decrease from 7.7 (95% CI 4.0-11.4) to 0.7 (95% CI 0.0-1.9) between the first and the last 10-year period occurred among males aged 40-49 years (I, Table). This was mainly due to the decrease of supraglottic disease.

The highest incidence of supraglottic tumours was among males aged 65-69 years, while that of glottic lesions was in the age group 75-79 years (I, Fig. 3). The site-specific incidence rates for males indicate that the decrease of occurrence was largely due to the significant ($p<0.001$) diminishing of supraglottic cases (I, Fig. 4). A significant ($p=0.024$) decrease took place also in the incidence of glottic carcinoma after the year 1968. In the first 5-year period 1962-66, the glottic to supraglottic incidence ratio for males was 0.5:1 and had increased to 1.9:1 in 1987-91.

Risk factors (II, III)

Of the 258 patients (244 males and 14 females) whose smoking habits were recorded, 235 (91%) were regular smokers. This percentage remained the same over the study period. The proportion of smokers among male patients (92%) differed significantly ($p=0.026$) from that of females (71%). In both sexes the proportion of smokers was significantly higher among the patients than in the whole population. A significant ($p=0.025$) difference in the proportion of smokers was also found between supraglottic (96%) and glottic (88%) cases.

Consumption of alcohol was recorded only in 100 patients (31%). 37% of them were heavy drinkers, among whom supraglottic tumours were more common (49%) than glottic lesions (41%). Moderate/non-drinkers had a supraglottic tumour in 43% of cases and a glottic one in 56%. These differences were not statistically significant.

The socio-economic distribution of the 291 evaluable male patients differed significantly from that of the whole male population: there were 2.0 times (95% CI 1.5-2.6) more unskilled workers and 1.3 times (95% CI 1.1-1.6) more skilled and specialized workers among the patients. Socio-economic status affected also the site distribution significantly ($p=0.046$): the proportion of supraglottic tumours was 12% in managers and higher administrative personnel, 44% among lower administrative

personnel and skilled and specialized workers and 53% in unskilled workers.

Clinical presentation (III-V)

Symptoms

The symptom profile of the 301 evaluable patients with LSCC was markedly affected by tumour site (IV, Table 2). Hoarseness was more commonly associated with glottic and subglottic tumours, although it was the most frequent symptom also in supraglottic cases. Supraglottic tumours caused a markedly higher occurrence of sore throat, dysphagia, globus, otalgia and haemoptysis. Dyspnoea was most common in subglottic cases. These findings were independent of the differences in stage distribution between tumour sites. About 10% of patients having a supra- or subglottic lesion presented with a neck mass noticed by the patient, which was the only symptom in two cases.

Supraglottic tumours caused significantly ($p<0.001$) more symptoms (median 2) than glottic lesions (median 1). The number of symptoms increased along with stage regardless of tumour site. The median duration of symptoms was 4.2 months and it was not significantly affected by tumour site. Symptom duration was significantly longer in stage III-IV cases (median 4.7 months) than in stages I-II (median 3.8 months, $p=0.038$). A parallel but non-significant trend was also present separately in glottic and supraglottic cases. The median lengths of individual symptoms ranged from 1.0 month of haemoptysis to 4.1 months of hoarseness (IV, Table 3).

Tumour extent at diagnosis

There was a significant ($p<0.001$) difference in the T-distribution between supraglottic and glottic tumours so that 51% of glottic but only 14% of supraglottic lesions were T1, while T2 and T4 tumours were more common in supraglottic cases (III, Table 1). Of the 10 subglottic tumours, 5 were T2, 2 T3 and 3 T4. At the time of diagnosis, regional lymph node metastases were present in 21% of patients with a

supraglottic tumour but only in 2% of those with a glottic lesion. In one T2 subglottic case there was a N1 cervical metastasis. Four patients (two supraglottic and two glottic) had distant metastases at diagnosis. The proportion of T1-2 tumours decreased from 72% to 64% and that of T3-4 lesions increased from 28% to 36% from the first to the last ten-year period. This trend was found also separately among glottic and supraglottic cases, but it was not statistically significant.

Of the 76 patients with early glottic carcinoma treated by primary megavoltage radiotherapy since 1970, 58 had a T1a, 2 a T1b and 16 a T2 tumour. To further classify the extent of the disease, involvement of the anterior, middle and posterior third of each vocal cord was estimated separately (V, Table 2). T2 tumours affected the posterior third significantly (p=0.002) more often than T1 lesions. Seventeen T1 tumours and one T2 lesion were limited to only one vocal cord third. Of these 18 small tumours, 14 were in the anterior third and four in the middle part of the cord. None of these 76 patients had regional or distant metastases at the time of diagnosis and only two had a neck node relapse.

Pretreatment evaluation

In all 309 patients with records available in the hospital files, the diagnosis of laryngeal carcinoma was confirmed histologically. Table 4 summarizes the methods used to obtain the diagnostic biopsies.

Table 4. *Methods of obtaining the diagnostic biopsy*

Method	n	(%)
Indirect laryngoscopy, local anaesthesia	1	(0.3)
Fiberoscopy, local anaesthesia	3	(0.9)
Direct laryngoscopy, local anaesthesia	69	(22.3)
Direct laryngoscopy, general anaesthesia	29	(9.4)
Tracheostomy + direct laryngoscopy	8	(2.6)
Tracheostomy + microlaryngoscopy	14	(4.5)
Microlaryngoscopy, conventional intubation	61	(19.7)
Microlaryngoscopy, intratracheal jet ventilation	119	(38.5)
Bronchoscopy, general anaesthesia	1	(0.3)
Open biopsy	1	(0.3)
Obduction	3	(0.9)

In the early 1960s, most direct laryngoscopies were carried out under local anaesthesia. After the end of the 1960s, general anaesthesia was chiefly used. The first microlaryngoscopies were performed in 1968, and since 1971 microlaryngoscopy under general anaesthesia has been the main method for evaluating laryngeal tumours. Jet ventilation was first used in 1972, and after 1978 intratracheal jet ventilation has been the primary ventilation technique.

In 24 patients the first biopsy was unsuccessful and in 5 cases a third biopsy was required to confirm the diagnosis. Most (20) unsuccessful biopsies were obtained by direct laryngoscopy in local anaesthesia, and the proportion of failures (23%) was significantly higher than that of direct laryngoscopy in general anaesthesia (7%, $p=0.047$) and microlaryngoscopy with conventional endotracheal intubation (3%, $p<0.001$) or intratracheal jet ventilation (3%, $p<0.001$). Due to the small number of failures, the differences in the percentage of failed biopsies between the other methods of laryngoscopy could not be analysed.

The extent of the tumour was evaluated by laryngeal tomography in 3 patients and in 3 cases CT was used. One patient underwent ultrasonography of the neck during the primary evaluation of the disease.

Treatment modalities (III, V)

Of the 303 evaluable patients with LSCC, 166 (55%) were primarily treated by radiotherapy, 38 (12%) by surgery and 94 (31%) received combined therapy. Five patients (2%) did not get any curative treatment because of widespread disease, very poor general condition or death of other diseases before the beginning of the planned treatment. In five patients with advanced disease, chemotherapy was combined to the primary treatment.

Most early (T1-2) glottic tumours were treated by primary radiotherapy with salvage surgery for recurrent disease. Of the supraglottic T1-2 tumours, 38% were primarily irradiated while in 45% a supraglottic and in 17% a total laryngectomy was performed. In these early supraglottic cases, radiotherapy was often combined with the operative treatment, which usually also included a neck dissection. T3-4 tumours were mostly treated by total laryngectomy and neck dissection combined with radiotherapy. Of the 10 patients with subglottic disease, 4

had primary radiotherapy while 6 underwent total laryngectomy and neck dissection, in 5 patients combined with radiotherapy.

Radiotherapy

Radiotherapy was the only primary treatment of 166 patients and 94 were treated by combination of surgery and irradiation. Up to 1970, the radiotherapy was accomplished by 250 kV X-rays (69 patients). 1970-88 the irradiation was administered with a cobalt-60 unit (177 patients) and after that with a 5 MV linear accelerator (14 patients). Of the 166 patients treated with primary radiotherapy, 104 (63%) had a glottic T1 or T2 tumour and 27 (16%) a supraglottic T1-2 lesion. In general, irradiation was the primary treatment of T3-4 tumours only if they were considered inoperable or if the patient's general condition did not allow operation.

Eighty-two (96%) of the 85 glottic T1 and 22 (58%) of the 38 glottic T2 tumours were treated with primary irradiation. 28 patients (21 T1 and 7 T2) had X-ray therapy and in 76 patients (60 T1 and 16 T2) the newer techniques were used. In the 76 cases treated by the megavoltage techniques, the total dose ranged from 45 Gy to 70 Gy, normalized to minimum target-absorbed dose. 24 patients treated in the 1970s received hypofractionated therapy with a median total dose of 58 Gy and fraction size between 3.0 and 4.5 Gy. Since 1980 the total dose was mainly standardized to 64 Gy (range 60-70, median 64 Gy), given in 32 daily fractions. Except for three patients treated during the last years of the study period, radiotherapy was delivered by split-course technique with a pause of 1-3 weeks in the middle of the treatment. The duration of therapy ranged from 42 to 89 days (median 63 days).

Surgery

Total (n=84) and supraglottic (n=39) laryngectomy were the most common primary operations. In addition, 3 laryngopharyngectomies, 2 hemilaryngectomies and 2 chordectomies using thyrotomy approach were performed. In 2 patients, a neck dissection without any laryngeal operation was carried out in addition to radiotherapy. Of the 38 patients whose only primary treatment was surgery, 26 had total laryngectomy, 11 supraglottic laryngectomy and 1 hemilaryngectomy. In two patients a Provox® voice prosthesis was installed during total laryngectomy.

A neck dissection was included in 117 of the 132 primary operations. 93 patients underwent modified radical neck dissection with preservation of the accessory nerve; the nerve was sacrificed in only 21 patients. In addition, 3 supraomohyoid neck dissections were performed. 99 (85%) of the neck dissections were elective, i.e. there was no clinical evidence of lymph node involvement.

Combined treatment

Out of the 94 patients treated with a combination of surgery and irradiation, 36 had preoperative and 51 postoperative radiotherapy. In 7 cases, sandwich therapy (combination of pre- and postoperative irradiation) was given. Preoperative radiotherapy was used particularly in the 1970s and early 1980s, and often the final decision on operative treatment was made according to radiation response in the middle or at the end of the radiotherapy.

Prognosis (III-V)

The overall 5-year disease-specific survival was 77%. In 1962-1971, the survival was 77%, in 1972-1981 73% and in 1982-1991 83%. These differences were not statistically significant (p=0.391). When the 25 incompletely treated patients were included in the analysis, the overall 5-year disease-specific survival was 69%.

Tumour and patient factors

The 5-year disease-specific survival was 81% in glottic and 71% in supraglottic disease. This difference was not statistically significant (p=0.103, III, Fig. 1). Also when the survival was analysed by T-category, no significant difference was found between the two sites (III, Table 2). When patients with a transglottic tumour were excluded from the analysis, the prognosis was significantly better in glottic than in supraglottic disease (5-year survival 89% vs. 72%, p=0.005). This significance was, however, lost when the survival was adjusted for T-category.

The disease-specific survival decreased significantly with advancing T-category ($p<0.001$, Fig. 1) and stage ($p<0.001$). The 5-year survival of N0 patients was 81% and that of N+ patients 33% ($p<0.001$). These findings were significant also when adjusted for tumour site.

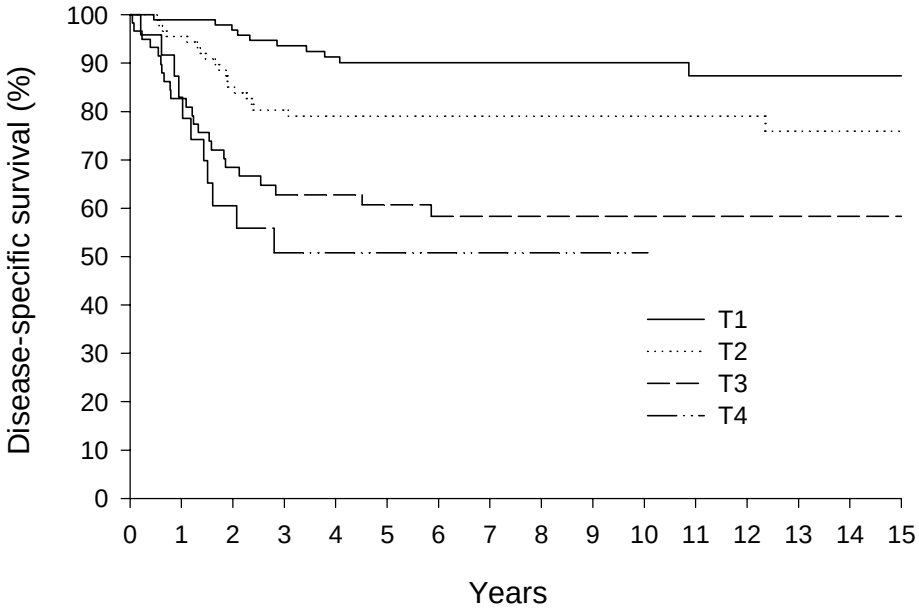

Figure 1. Disease-specific survival by T-category

Among the 76 patients with a T1-2 glottic tumour treated with megavoltage radiation since 1970, the 5-year locoregional control rate was 85% in T1 and 48% in T2 disease (V, Table 3). The 5-year disease-specific survival was 91% in T1 and 69% in T2 patients. Several tumour-related variables had a significant effect on locoregional control and survival in univariate analyses (V, Table 4). In the multivariate analysis of primary locoregional control, only the number of vocal cord thirds involved (V, Fig. 1) had significant prognostic value (HR 3.2, 95% CI 1.8-5.8, $p<0.001$). Extension of the tumour to the posterior vocal cord third (HR 8.4, 95% CI 1.0-69.5, $p=0.049$, V, Fig. 2) and higher T-category (HR 3.0, 95% CI 0.9-10.2, $p=0.079$) were connected with poorer prognosis in the multivariate analysis of disease-specific survival.

Age, socio-economic status or smoking habits of the patients did not affect the disease-specific survival significantly. None of the 14 female patients treated with curative intent died of their carcinoma. However, the difference in 5-year disease-specific survival between males (75%) and females (100%) just failed to reach statistical significance (p=0.053).

Multiple symptoms and presence of dyspnoea, globus, haemoptysis or a neck mass noticed by the patient indicated significantly worse prognosis. The duration of the symptoms did not have prognostic significance. When symptom number and presence of the above-mentioned individual symptoms were analysed by stage they lost their significance, which indicates that their impact on survival was merely due to the association with stage.

Treatment factors

The prognostic impact of the primary treatment was analysed using a Cox regression model including covariates T-category, N-status (N0/N+) and treatment modality (radiotherapy/surgery/combined). Patients treated with a combination of surgery and radiotherapy had significantly better disease specific survival (HR 0.55, 95% CI 0.31-0.97, p=0.042) than those treated with radiotherapy only (HR 1). No significant difference was found between radiotherapy and surgery or between surgery and combined treatment.

The 5-year locoregional control rate (68% vs. 85%, p=0.071) and disease-specific survival (83% vs. 91%, p=0.163) of the 28 patients with early glottic carcinoma treated by X-rays were inferior to those irradiated with the megavoltage techniques. Among the 60 patients with glottic T1 carcinoma treated with primary megavoltage radiation, longer duration of the treatment indicated worse locoregional control (HR 1.1, 95% CI 1.0-1.3, p=0.019) and poorer survival (HR 1.2, 95% CI 1.0-1.3, p=0.038) in multivariate analysis. Other treatment factors did not affect the prognosis significantly.

Multivariate analysis of prognostic factors

The prognostic factors were further evaluated by multivariate Cox regression analysis of disease-specific survival including the variables age, year of diagnosis, tumour site, T-category, N-status (N0/N+), treatment modality (radiotherapy/surgery/combined) and mode of

radiotherapy (X-ray/other/none). Treatment modality ($p=0.042$), T-category ($p<0.001$) and N-status ($p=0.002$) affected the survival significantly. Treatment modality lost its significance when the subglottic cases were excluded from the analysis.

DISCUSSION

Occurrence

Since the Finnish Cancer Registry was established, the annual age-adjusted incidence of laryngeal cancer in males seemed to rise from 5.6/100,000 in 1953 to the highest figure of 7.6/100,000 in 1968. It is, however, possible that in the early years both the diagnostics and the recording of cancers were less accurate and some cases may have been missed. The most striking incidence decrease, from 7.4 to 5.2/100,000/year, occurred in 1970-1974. Thereafter this decline has slowed, and according to recent statistics the annual male incidence seems to have settled at around 3/100,000 (Finnish Cancer Registry 1989-1997). The male incidence has thus decreased by about 60% in 25 years. In women the occurrence has remained practically unchanged, the mean annual age-adjusted incidence being 0.3/100,000. In the present patient population from the Tampere University Hospital the incidence trend was parallel with the nation-wide figures, but the numbers were somewhat lower: among men the highest 5-year average incidence was 6.7/100,000 in 1967-71 and the lowest 2.6/100,000 in 1987-1991 while in women the mean incidence was steadily 0.2/100,000/year. In most previous studies, increasing occurrence trends have been observed among both sexes, and often the female incidence has increased faster (Ayiomamitis 1989, DeRienzo et al. 1991, Robin et al. 1991). Even though in the present series and in Finland as a whole the female incidence has remained unchanged, the prominent decrease of the occurrence among men has caused a marked decrease of the male to female incidence ratio also here.

In the 1960s the male incidence of laryngeal cancer was more than three times higher in Finland than in the other Nordic countries (Mårtensson 1975, Engeland et al. 1993). This was mainly due to the higher number of supraglottic cases (Mårtensson 1975). Although comprehensive information about the site distribution for the whole country is not available, especially supraglottic cancer seems to have decreased drastically, leading to a reversal of the glottic to supraglottic incidence ratio (Mäkitie et al. 1999). In the present series two-thirds of the tumours were supraglottic in the first 5-year period, but after that the glottic to supraglottic ratio gradually reversed. The decline of the overall

incidence was largely due to the decrease of supraglottic cases, even if the occurrence of glottic carcinoma also decreased significantly.

The finding of distinct supraglottic dominance in previous Finnish studies (Lauerma 1967, Taskinen 1969) has later been questioned due to the risk that advanced transglottic tumours of glottic origin have been incorrectly classified as supraglottic (Mäkitie et al. 1999). Although difficulties and variation in the classification of advanced tumours undoubtedly exist, the present findings indicate an indisputable decrease of the proportion of supraglottic tumours also when transglottic lesions were excluded. On the other hand, the proportion of transglottic tumours among glottic and supraglottic cases has remained unchanged. Consequently, it seems very unlikely that the observed shift from supraglottic to glottic predominance among the present patients would have been entirely due to a bias in the classification of the tumours.

As with all the other populations studied, there was a distinct male predominance in the present patient cohort. The overall age distribution, with a median of 63 years, was also similar to previous findings. The relative frequency of supraglottic cancer has often been reported to be higher in women (Stephenson et al. 1991, Harris et al. 1993, Grénman et al. 1996) and the proportion of female patients has sometimes been greater in younger age groups (Lauerma 1967, Rothman et al. 1980, Robin et al. 1991). These observations could not be confirmed in the present study, but the number of female patients was too low for any definitive conclusions. In accordance with some earlier reports (Lauerma 1967, Stephenson et al. 1991, León et al. 1998), supraglottic disease seemed to be more common in younger patients, although no significant difference in the median age was found. As in previous studies, squamous cell carcinoma was by far the most common histological finding (Alexander and Cassady 1966, Marck and Lupin 1989, Krecicki et al. 1998).

Risk factors

Smoking and high alcohol consumption are generally accepted as the major risk factors for laryngeal cancer (IARC 1986, IARC 1988). The role of alcohol has been considered important especially in the etiology of supraglottic carcinoma. This is supported by the fact that in France, Italy, Spain and Uruguay where the consumption of alcohol—especially

wine—is high, high occurrences of laryngeal carcinoma with supraglottic dominance have also been found (De Stéfani et al. 1985, De Stéfani et al. 1987, Tuyns et al. 1988, Silvestri et al. 1992, Tuyns 1994). On the other hand, the use of the more carcinogenic black tobacco has also been popular among these populations with Latin ancestry (De Stéfani et al. 1985, De Stéfani et al. 1987, Tuyns et al. 1988). The smoke of cigarettes made of this air-cured tobacco is strong and alkaline, and therefore its contact with the supraglottic structures may be longer than that of blond tobacco smoke (De Stéfani et al. 1987). The smoke of black cigarettes is obviously also more carcinogenic than that of blond cigarettes (De Stéfani et al. 1987, Tuyns et al. 1988).

Favourable changes in smoking habits, i.e. decreased frequency of smoking and abandonment of "Russian-style" cigarettes, are most probably the main reason for the remarkable decrease of laryngeal cancer among Finnish males during the past 30 years. This is in line with the finding that lung cancer—also a strongly tobacco-related disease—has shown a similar incidence trend in Finland (Finnish Cancer Registry 1989-1997, Engeland et al. 1993). The pronounced decrease of the proportion of supraglottic tumours conflicts with the finding that alcohol is an important factor in the etiology of supraglottic cancer, because in Finland the total consumption of alcohol has increased markedly since the late 1960s. However, the consumption is even nowadays lower in Finland than in France, Italy and Spain (Statistics Finland 1998). The improved standard of living, favourable dietary changes, and perhaps alterations in Finnish sauna habits may also have affected the occurrence. The role of the standard of living in the etiology of particularly supraglottic cancer is supported by the present finding of significantly higher proportion of supraglottic tumours in lower socio-economic groups, which is in agreement with the report of De Stéfani et al. (1985) from Uruguay. As in some previous studies, low socio-economic status was also connected with increased overall risk of laryngeal cancer (Wynder et al. 1976, Elwood et al. 1984, Kleinsasser 1988). The most obvious reasons for the impact of socio-economic status are differences in smoking, drinking and dietary habits, but other factors may also have some impact. The possible role of sauna habits is based on the finding that the air of smoke saunas and pre-heated saunas contains high concentrations of carcinogenic polycyclic aromatic hydrocarbons (PAH), resulting in increased inhalation exposure to these compounds when bathing in these saunas regularly (Häsänen et al. 1983). Lower concentrations of PAH were found in saunas heated by a continuous burning of wood. This type of sauna, together with the electric sauna, has

become more common after the 1950s. Indoor pollution by emissions of stove-heating or cooking with oil, coal, gas and wood has also been found to increase the risk of laryngeal cancer (Dietz et al. 1995). In the first half of the twentieth century stove-heating with wood and wood-heated cookers were very common in Finland. Later wood-heating has mostly been replaced by central or electric heating and electric cookers.

Obviously the causes of the previous high occurrence of supraglottic cancer in Finland have been at least partly different from those of the Mediterranean and Latin American areas where the high consumption of alcohol is undoubtedly an important risk factor (De Stéfani et al. 1985, De Stéfani et al. 1987, Tuyns et al. 1988, Silvestri et al. 1992, Tuyns 1994). It may be speculated that the supraglottic larynx is more sensitive to heavy exposure to inhaled, as well as ingested, carcinogens than the vocal cords. Thus the occurrence of supraglottic carcinoma may be more dependent on variations in the predisposing factors. This idea is supported by the finding that a high occurrence of laryngeal cancer is usually connected with a high proportion of supraglottic cases, while the incidence of glottic cancer shows less variation (De Stéfani et al. 1985, De Stéfani et al. 1987, Tuyns et al. 1988, Silvestri et al. 1992, Tuyns 1994).

Clinical presentation

The symptom pattern of the present patients is consistent with previous reports (Kaufman et al. 1980, Marck and Lupin 1989, Merletti et al. 1990, Dolan et al. 1998). Hoarseness was distinctly the most common symptom regardless of tumour site. It was more prevalent in glottic and subglottic cases, but it was also the leading symptom in supraglottic disease. Spread of the tumour to vocal cord(s) increased the frequency of hoarseness in supraglottic disease. Other symptoms were mainly associated with supraglottic tumours and more advanced glottic lesions. Sore throat was the second most common symptom in supraglottic disease; among stage I cases it was even more prevalent than hoarseness.

The proportion of advanced stage lesions was distinctly higher among patients with a supraglottic tumour, but there was no considerable difference in symptom duration between supraglottic and glottic cases. This supports the common opinion that the symptoms

appear later in supraglottic cancer (Kleinsasser 1988). Opposite to several previous reports, in the present study there was a significant positive association between symptom duration and tumour stage at diagnosis (Kaufman et al. 1980, Pera et al. 1986, Barra et al. 1990, Merletti et al. 1990, Vernham and Crowther 1994, Dolan et al. 1998). In addition to differences in intrinsic aggressiveness of the neoplasms (Kaufman et al. 1980, Barra et al. 1990, Vernham and Crowther 1994), recall bias by the patients and inaccurate recording of the symptoms are obvious contributors to the usual lack of association between symptom duration and the stage of the disease at the time of diagnosis (Kaufman et al. 1980, Barra et al. 1990, Dolan et al. 1998). It is easy to understand that a patient presenting with an advanced tumour and prominent symptoms does not always remember the onset of the minor early symptoms. Consequently, symptom duration reported by the patient may—especially in advanced cases—be unreliable and does not indicate the real duration of the disease. Furthermore, the symptom pattern of rapidly advancing tumours may differ from that of less aggressive lesions (Austin and Dunn 1980, Merletti et al. 1990).

In parallel with previous studies, glottic tumours were more often found at an early stage and patients with a supraglottic tumour presented more often with neck node metastases (Stell 1990b, Shah et al. 1997, Krecicki et al. 1998). Presence of hoarseness even with small vocal cord tumours is a major contributor to the early detection of glottic cancer. In addition, glottic carcinomas almost always arise from the anterior half of the vocal cord (Kleinsasser 1988) where the subepithelial lymphatic network is sparse (Werner et al. 1990). This results in a low frequency of nodal and distant metastases, especially in early glottic carcinoma. Among the 76 T1-2 glottic cancer patients of the present series treated with primary megavoltage radiotherapy, the anterior third of the vocal cord(s) was invaded by the tumour in 90%, and the middle and posterior thirds in 80 and 47%, respectively. All 18 tumours limited to one vocal cord third were on the anterior or middle thirds. None of the 76 patients had nodal or distant metastases at the time of diagnosis.

Diagnostics

Screening of laryngeal carcinoma, or even of all head and neck cancers together, seems not rational because of the relatively low incidence, even if focused on the high risk population (Kleinsasser 1988). The weak correlation between the symptom duration and the stage at diagnosis has also led to scepticism concerning possibilities to increase the proportion of tumours found at early stages and thus improve the cure rates (Kaufman et al. 1980, Vernham and Crowther 1994, Dolan et al. 1998). It has also been stated that the early detection of vocal cord carcinoma has increased considerably but seems to have reached a plateau, and further progress of the early diagnoses is restricted by the fact that only a proportion of the tumours can be diagnosed early due to the differences in their intrinsic aggressiveness (Kleinsasser 1988). The same author considers that supraglottic carcinomas are symptomless over a long period and continue to be diagnosed in an advanced stage with only occasional early diagnoses. In the present study the proportion of glottic tumours diagnosed at stages I-II was about 75% and even in supraglottic cases this proportion was over 50%. The fact that the percentage of early stage cases decreased during the study period in spite of the improved standard of living and increased availability of health care services supports the opinion that the early detection of laryngeal cancer is difficult to improve. However, 1/3 of the present patients had had symptoms for over 6 months and 1/4 of advanced (stage III-IV) cases for over one year. The delay by at least the patients with a long symptom duration might be shortened by appropriate information to the high risk group, i.e. middle-aged (male) smokers. Furthermore, the importance of prompt and adequate laryngeal examination of patients with prolonged hoarseness or other symptoms suggestive for laryngeal cancer should be emphasized to primary health care physicians.

In the present patient population direct laryngoscopy under local anaesthesia was the primary procedure in taking diagnostic biopsies in the early 1960s. Most unsuccessful biopsies were obtained by this method, and the proportion of failures (23%) was significantly higher than later when the (micro)laryngoscopies were performed under general anaesthesia. Due to the small number of inadequate biopsies, differences between conventional intubation and jet-ventilation or between direct laryngoscopy and microlaryngoscopy could not be evaluated. Because CT and MRI were not available during the study period, laryngoscopy was

the main method of evaluating the extent of the tumours. The neck status was evaluated only by palpation.

Prognosis

In accordance with some earlier findings, the female patients of the present study had better prognosis than men (Kowalski et al. 1991, Boffetta et al. 1997). This difference was, however, not statistically significant. Age, socio-economic status or smoking habits did not affect the prognosis.

A high number of symptoms has been found to predict poor prognosis in neuroblastoma (Berthold et al. 1997), and in colorectal (Polissar et al. 1981), lung (Coy et al. 1981) and nasopharyngeal (Neel et al. 1985) cancers. In the present study a positive correlation between the number of symptoms and tumour stage was found. The survival analysis revealed that the higher the number of symptoms the poorer the prognosis, but in the multivariate Cox regression analysis symptom number did not have an independent prognostic value. The presence of certain individual symptoms also had an adverse prognostic effect in univariate analysis, but due to strong association with stage this effect disappeared in multivariate analysis. Like in previous studies, the duration of the symptoms did not have any prognostic significance (Kaufman et al. 1980, Pera et al. 1986, Barra et al. 1990, Vernham and Crowther 1994, Dolan et al. 1998).

Supraglottic tumours are generally considered to have poorer prognosis than glottic ones (Lauerma 1967, Stell 1990b, Silvestri et al. 1992). This is, however, mostly due to the more advanced stage and the higher metastasizing potential of supraglottic tumours (Lauerma 1967, Stell 1990b, Shah et al. 1997). In addition, according to the current T classification, much larger supraglottic than glottic tumours can be classified as T1, which militates against supraglottic lesions (Kleinsasser 1988, Stell 1990b). The present results are in agreement with previous multivariate analyses, where the tumour site did not have an independent impact on prognosis (Gavilán et al. 1987, Stell 1990b).

Apart from T-category and N-status, treatment modality was identified as an independent prognostic factor in the multivariate Cox regression analysis of disease-specific survival among the present patients. Those primarily treated with a combination of surgery and radiotherapy had

significantly better survival than patients treated with only radiotherapy. However, treatment modality lost its significance when the 10 subglottic cases were excluded from the analysis, which reduces the value of this finding. In addition, there are possible confounding factors related to treatment selection, e.g. patients with a tumour considered inoperable or those with poorer general condition are more likely to have been treated by radiotherapy instead of combined treatment. Consequently, no definitive conclusions regarding the efficacy of the various treatment modalities can be drawn.

In accordance with previous findings (Pera et al. 1986, Kowalski et al. 1991, Pradier et al. 1993), T-category and N-status were the most important prognostic indicators in the present study. In the future, the novel biomarkers (Cappellari 1997) and other variables like tumour volume (Lo et al. 1998, Mukherji et al. 1999) may improve the prognostic evaluation and selection of the optimal treatment for patients with laryngeal cancer.

Radiotherapy outcome of early glottic carcinoma

Due to a high cure rate associated with low morbidity and good voice quality, radiotherapy has generally been the treatment of choice in early glottic carcinoma (Pellitteri et al. 1991, Burke et al. 1997, Le et al. 1997), but conservative surgery has also been advocated (Kleinsasser 1988, Thomas et al. 1994, Osguthorpe and Putney 1997). More recently, endolaryngeal laser surgery has become a frequently used treatment modality which compares well with radiotherapy in tumour control (Eckel and Thumfart 1992, Steiner 1993, Davis 1997). Also the voice quality after laser surgery appears as good as in irradiated patients (McGuirt et al. 1992, Steiner 1993, McGuirt et al. 1994), although findings in favour of radiotherapy have also been presented (Epstein et al. 1990, Rydell et al. 1995). In the present series 96% of glottic T1 and 58% of glottic T2 tumours were treated with primary irradiation. Up to 1970, 250 kV X-rays were used and after that the irradiation was administered with a cobalt-60 unit or with a 5 MV linear accelerator. Treatment outcome of the 76 patients treated with the megavoltage techniques was studied in detail and the following discussion applies to this group of patients only.

In most previous studies the locoregional control rate of T1 glottic cancer treated with primary radiotherapy has varied between 80 and 95% (Cellai et al. 1990, Viani et al. 1991, Klintenberg et al. 1996) and disease-

specific survival between 92 and 100% (Cellai et al. 1990, Pellitteri et al. 1991, Kanonier et al. 1996). Patients with T2 disease have a less favourable outcome with local control rates mainly between 64 and 88% (Amornmarn et al. 1985, Cellai et al. 1990) and survival after salvage 73 to 94% (Cellai et al. 1990, Howell-Burke et al. 1990). The present 5-year locoregional control rate of 85% for T1 is fairly in line with these figures but 48% for T2 disease is clearly inferior. The 5-year disease-specific survival of 91% for T1 cases in the present series compares quite well with previous findings (two patients refused salvage surgery), but the 5-year survival of 69% in T2 disease is less satisfactory, even if the number of patients was small and only 6 out of 9 patients with recurrence were salvaged.

The radiotherapy parameters fluctuated during the study period, but they had no statistically significant effect on locoregional control or survival in the analyses comprising both T1 and T2 patients. In T1 cases the duration of the radiotherapy was, however, a significant factor in the multivariate analyses of locoregional control and survival. All but three of the patients received split-course therapy, which was a common treatment regimen of that time, and the median duration of the treatment was 63 days. Several reports have shown the unfavourable effect of interruptions and prolongation of the treatment time on radiotherapy outcome (Klintenberg et al. 1996, Le et al. 1997, van der Voet et al. 1998). Thus the split-course regimen with longer treatment times probably explains the reasonably low cure rate in T2 cases. The total irradiation dose (Barton et al. 1992, Sakata et al. 1994, Le et al. 1997) and fraction size (Burke et al. 1997, Le et al. 1997) may also affect the treatment outcome. Especially in T2 disease, high total doses of 66-70 Gy have been proposed to result in better outcome (Kanonier et al. 1996, Le et al. 1997). The total doses of the present patients were mostly lower.

Several factors reflecting tumour location and extent have been reported to possess prognostic value in patients with early glottic carcinoma (Sakata et al. 1994, Klintenberg et al. 1996, Burke et al. 1997). In the present series, higher T-category, the greater number of vocal cord thirds involved, extension to the posterior end of the vocal cord and supraglottic spread had significant unfavourable impact on both primary locoregional control and disease-specific survival in the univariate analyses. Impaired vocal cord mobility had a significant effect only on survival, and involvement of the anterior commissure on locoregional control. In the multivariate analysis of locoregional control, all tumour-related covariates except the number of vocal cord thirds involved lost their significance. The significance of the number of involved thirds also

in the separate analysis of T1 cases shows that its impact is not merely because of the association with T-category. This finding suggests that the conventional T-classification is not invariably the best indicator of the real nature of the disease; a classification based on the actual size of the tumour could have a better prognostic value (Harrison 1979, Kleinsasser 1988, Kleinsasser 1992). In the multivariate analysis of disease-specific survival, involvement of the posterior vocal cord third had significant prognostic value together with T-category. Even though these two variables were clearly correlated, the significance of posterior third involvement in the separate analysis of T1 cases implies that its influence is at least partly independent from the T-category. Because the glottic tumours in the first place originate from the anterior part of the cord, extension of the tumour to the posterior third reflects mainly tumour size, but its impact might partly be due to the greater risk of lymphatic metastases from the posterior portion of the vocal cord. This assumption is based on the finding of Werner et al. (1990) that the subepithelial lymphatic network is most dense in the arytenoid region and diminishes towards the anterior part of the vocal cord. In the present series, two tumours (one in each T-category) recurred lethally with cervical node metastases. In both cases the primary lesion extended to the posterior third of the cord. Because of the minor number of patients with cervical metastases this interpretation is, however, highly hypothetical.

In addition to tumour eradication, preservation of satisfactory laryngeal function is an important aspect of laryngeal cancer treatment. In the present series, 87% of T1 patients but only 44% of T2 patients retained their larynxes. The result of T1 cases is comparable with previous findings of 85-100% (Amornmarn et al. 1985, Pellitteri et al. 1991, Kanonier et al. 1996), but in T2 disease laryngeal preservation mostly varies between 74 and 88% (Amornmarn et al. 1985, Howell-Burke et al. 1990, Pellitteri et al. 1991). In 70% of the present patients the voice was estimated as normal or nearly normal, 5% had severe and 25% moderate dysphonia after curative primary radiotherapy. These figures are in accordance with some previous findings (Benninger et al. 1994, Le et al. 1997), but on the other hand the voice quality has often been described to be good in over 90% of patients (Amornmarn et al. 1985, Pellitteri et al. 1991, Burke et al. 1997). As compared with previous reports (Klintenberg et al. 1996, Burke et al. 1997, Le et al. 1997), the present frequency of serious complications was reasonably high, most probably due to the large fraction sizes used in the 1970s. Only one patient treated in the 1980s with fractions of 2.0 Gy developed chondroradionecrosis.

CONCLUSIONS

The age-adjusted annual incidence of laryngeal cancer among males decreased by over 60% during the study period of 1962-1991. This phenomenon was largely due to the decrease of supraglottic disease though the occurrence of glottic carcinoma also diminished significantly. Although the female incidence remained unchanged, the male to female ratio decreased distinctly due to the marked incidence decline in men. The supraglottic to glottic ratio changed from 2/3 to 1/3 during the study period.

Smoking and low socio-economic status were significantly associated with higher risk of laryngeal cancer. Favourable changes in the smoking habits of Finnish men seem to be the most important reason for the declining occurrence, although other factors may also have contributed to this trend.

There were considerable differences in the epidemiology and clinical presentation of glottic and supraglottic carcinoma. A significantly higher proportion of supraglottic tumours was found among patients younger than 50 years and in lower socio-economic groups. Patients with supraglottic carcinoma presented more often with advanced tumours and neck node metastases. Tumour site did not have independent prognostic value.

The symptom profile was markedly affected by location of the tumour. Hoarseness was significantly more common in glottic disease and other symptoms were more prevalent in supraglottic cases. Patients with a supraglottic tumour also had more symptoms than those with a glottic lesion. A significant positive association between the duration of the symptoms and tumour stage was found. None of the symptom-related variables had independent effect on prognosis.

Among patients with early glottic carcinoma treated by primary megavoltage radiation since 1970, the prognosis was significantly better in T1 than in T2 disease. In the multivariate analysis of primary locoregional control, only the number of vocal cord thirds involved had independent prognostic value. Extension of the tumour to the posterior vocal cord third and higher T-category signified poorer disease-specific survival. Although the prognostic significance of treatment duration could be demonstrated only in T1 cases, the use of split-course regimen seems also to be a major contributor to the relatively low local control rate in T2 disease.

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