Carcinoma of the Larynx

Goro MOGI

Department of Otolaryngology, Yamaguchi University School of Medicine
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Etiology

Of course, the etiology of the laryngeal cancer as well as any other cancers remains an enigma, but there is a number of carcinogenic agents for this condition. These are tobacco, alcohol, nutritional deficiency, voice strain, poor dental hygiene, tuberculosis, syphilis, radiation to the neck, nasal obstruction and industrial exposure (metal dust, wood dust, isopropyl oil). However, other than tobacco data, these are not based upon statistically significant results, according to Wynder et al.[1)]

It has been well known that tobacco is etiological factor in cancer of the lung, upper respiratory-tract and oral cavity. Wynder et al[1)] described on in their epidemiological study of the etiology of cancer of the larynx, which consisted of an analysis of 209 white males with cancer of the larynx in comparison with a control group composed of 209 patients with cancer of the head and neck and with that of 132 patients with pulmonary cancer, that the relative risk for laryngeal cancer increases in proportion to the amount of tobacco smoked, paralleling pulmonary cancer, and on that cigar and pipe smokers have a greater risk for laryngeal cancer than for pulmonary cancer. Dunn et al[2)] noted that, out of 172 patients with laryngeal cancer, 157 (91.3 %) were cigarette smokers, 11.6 (6.4 %) pipe or cigar smokers and only 4 (2.3 %) nonusers. They concluded that tobacco is a major etiologic agent in the production of cancer of the upper respiratory-tract.

Jackson[3)] stated "Precancerous condition is present in probably 75 to 80 percent of the laryngeal cancer. Many authors have emphasized the importance of precancerous lesions in the development of laryngeal cancer[4)]. Leucoplakia or keratosis plays a role of precancerous condition in the laryngeal cancer. Friedberg et al[5)] found of 31 patients with cordal carcinoma, 19 (61 %) had definite evidence of leucoplakia, and who were excessive smokers. Clerf et al[6)] observed on the similar relationship between leucoplakia and the excessive used of tobacco.

Thus, if smoking is accepted as an etiologic factor in leucoplakia or keratosis, it may also be regarded as a factor in the development of cancer.

There are reports to exhibit relation between the bidi smoking and betal nut chewing and laryngeal cancer.[1)7)] The bidi is made by rolling tobacco flakes

in a rectangular piece of dried leaf of temburni (Diospyros melanoxylon). The betal nut is the fruit of the areca or betal palm (Areca catechu). Both is commonly used in India.[8]

Alcohol has also been suspected of playing one of the important roles in the development of laryngeal cancer. From the study of Wynder and his coworkers,[1] laryngeal cancer patients (especially extrinsic cancer) drank significantly more alcohol than pulmonary cancer patients or the control group. They noted that a significant number of smokers who are nondrinkers or light drinkers develop laryngeal cancer, but same cannot be demonstrated for drinkers. This evidence supports a hypothesis that smoking initiates and alcohol consumption promotes cancer of the larynx.

The possible relationship of sideropenic dysphagia (Plummer-Vinson syndrome) and extrinsic cancer of the larynx in women has been written by Waldenström[9] and Jacobsson.[10] In the study of Wynder et al[1], the Swedish data on extrinsic cancer of the larynx in women showed a relation to dietary deficiencies that lead to sideropenic dysphagia predisposing to extrinsic cancer of the larynx, which could not be demonstrated for American data.

Piquet[11] mentioned that tuberculosis, syphilis, radiation and even misuse of the voice are blamed for laryngeal cancer, even though Wynder's et al study[1] indicated that such factors are of little importance.

In Japan[12], eight cases have been reported with laryngeal cancer found in mustard gas poisoning. These patients had been working in a former Japanese army poison gas manufacturing factory located on a small island of Japan during world war 2, mainly producing mustard gas. The bulk of these cancers originated from the supraglottic region. No glottic cancer was encountered. In former time, the possibility that irritating mustard gas play a part in producing cancer was suggested by Orton.[34]

Reviewing literatures concerning the etiology of laryngeal cancer, it becomes obvious that tobacco smoking and alcohol consumption by smokers have a greatest risk for development of the cancer, however these are not specific for laryngeal cancer but responsible for other respiratory or alimentary tract. Another factors suspected of the causing of laryngeal cancer are not important except for a few special factors.

Classification

First attempt at classification of laryngeal cancer was made by Krishaber[13] in 1879, who separated laryngeal tumors into two main groups; intrinsic and extrinsic. The intrinsic cancer involves tumors on the laryngeal surface of the epiglottis and on the true and false cords. Wynder et al[1] used this method. However, this classification is not favorable in a view point of pathology and therapy, today, therefore, it is decline.

Thomson[14)15)] classified into four main subdivisions; 1. intrinsic, 2. subglottic, 3. extrinsic and 4. mixed. He restricted the term of "intrinsic" to include only tumors occuring on the true and false cords and in the ventricle or the interarytenoid region, and differentiated the subglottic cancer from "the intrinsic" classified by Krishaber, because of its different behavior.

Semon[16)] introduced the term endolaryngeal for all tumors within the larynx. Walsh,[17)] in 1947, proposed the following classification;

1. Intrinsic: A tumor confined to the true vocal cord only which must be movable.
2. Endolaryngeal: All tumors within the laryngeal box; that is tumors that involve the ventricle, false cords, and/or fixation of the vocal cord.
3. Subglottic: A primary tumor that arises just beneath the true vocal cords. (Ogura[18)]) gave some additional explanations which are that such a tumor is extensive when it involves the true vocal cord and that a true cord carcinoma that extends supraglottic and/or subglottic is no longer intrinsic.
4. Extrinsic or extralaryngeal: A primary lesion that involves the epiglottis, aryepiglottic fold, or pyriform sinus. Walsh designed this classification because the lymphatics in the true vocal cord are scanty, while those of any part of the larynx other than the true cord are abundant. Ogura[18)19)] supported and employed this classification,

Friedberg et al[5)] modified Walsh's classification to avoid varied interpretations of the term "intrinsic carcinoma". The modified classification is that 1. cordal carcinoma(occurs in true cords, with normal mobility), 2. endolaryngeal carcinoma (occurs in a true cord, with limitation of the mobility or fixation; ventricle, false cord or early subglottic invasion), 3. subglottic, and 4. extracordal or extrinsic carcinoma (occurs in the epiglottis, arytenoid, aryepiglottic fold or pyriform sinus).

Ogura et al[38)] proposed clinical, pathological and larynogographic classification which are follows:

1. Glottic — cancers limited to the true cord.
2. Infraglottic — cancers of the subglottis and glottis.
3. Supraglottic — cancers involving the false cord, fixed and free portion of the laryngeal surface of the epiglottis.
4. Transglottic — cancers that cross the ventricle, thus involving two or three of the above sites, the rare ventricular tumor is included in this group. These sites are illustrated on Fig. 1.

In classifications of laryngeal cancers mentioned above, full accord on terminology has not yet been reached. In some instances, old classification, "intrinsic" involves all tumors arising in the laryngeal box. More recently "intrinsic" is used for tumors occuring on the true and false cords, and in the ventricle or interarytenoid region, and most recently it means tumors confined to the true

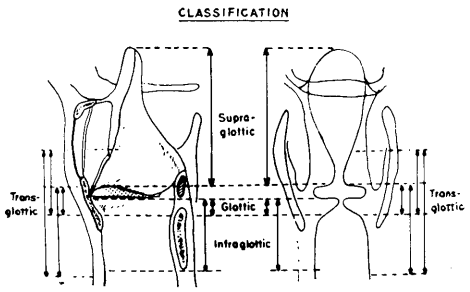

Fig. 1. Clinical, pathological and laryngographic classification proposed by Ogura.

cord only with good its mobility.

Recently an effort toward establishing a practical system of classification and staging of cancer of the larynx has been carried out in North America. This is the "Task Force on Larynx", a subcommite on Cancer Staging and End Results Reporting.[20] The classification proposed by the Task Force makes use of the T.N.M. system which was advocated by the Committe on Clinical Stage Classification and Applied Statistics of International Union Against Cancer in 1954 as an universal method of assessment for the clinical "Staging" of cancer at certain sites. This system has already been applied clinically in the study of other types of malignant disease such as the uterine cervix and breast. The T.N.M. system serves to define the extent of the primary tumor by the letter T, with an appropriate numerical suffix (T_1, T_2, T_3 or T_4), the status of the regional lymph nodes by the letter N (N_0, N_1, N_2, N_3) and the presence or absence of distant metastasis by the letter M (M_1 or M_0).

This method of classification for the larynx, pharynx, buccal cavity and bladder as well as for the breast has been under an international trial period of five years from Jan. Ist, 1963, by recommendation of the U.I.C.C.. U.I.C.C. Clinical Stage Classification For Laryngeal Cancer[21] is shown in Tables 1 and 2. The table 1 shows the anatomical regions and sites of the larynx.

Table 1. Anatomical regions and Sites of the Larynx

Reginos	Sites
larynx	posterior surface of the epiglottis
supraglottic	ventricular bands
	ventricles
	arytenoids
glottic	vocal cords
	anterior and posterior commissures
subglottic	walls of the subglottis
marginal zone	tip of the epiglottis
	aryepiglottic folds
laryngopharynx	pyriform sinus
(hypopharynx)	postcricoid area
	posterior pharyngeal wall

Table 2. Classification

supraglottic	glottic	subglottic
T. primary tumor		
T_1. Tumor Confined to one anatomical site within the larynx		
Tumor confined to laryngeal surface of epiglottis, or to an aryepiglottic fold or to a ventricular cavity or a ventricular band	Tumor confined to one ord and mobility of cord remains normal	Tumor limited to one side of the subglottic region, exclusive of the under-surface of cord
T_2. Tumor confined to one anatomical region within the larynx		
Tumor involving the epiglottis, extending to the ventricular band	Tumor involving both cords with normal of one or both cords with fixation of cords	Tumor extending to two sides of subglottic region, exclusive of the under-surface of the cords
T_3. Tumor extending beyond one anatomical region but confined to the larynx		
Tumor of the epiglottis and/or ventricles or ventricular bands, and extending into the cords	Tumors extending from cords either to subglottic region or to supraglottic region, that is, to ventricular bands or ventricles	
T_4. Tumor extending beyond the larynx		
Tumor as in T_1, T_2 or T_3, but with direct extension to pyriform sinus, postcricoid region, vallecula, or base of tongue	Tumor as in T_1, T_2 or T_3, but with direct extension through cartilage to skin, to the pyriform sinus, or to the postcricoid region	Tumor as in T_1, T_2 or T_3, but with direct extension to trachea, skin or postcricoid region
N. Lymph nodes		
N_0. No lymph node palpable		
N_1. Homolateral movable lymph nodes		
N_2. Bilateral or contralateral mobable lymph nodes		
N_3. Homolateral or bilateral fixed lymph nodes		
M. Metastasis		
M_0. No evidence of distant metastasis		
M_1. Distant metastasis		

For reason of recognizing the practical day-to-day need for a simpler plan of classification than the unwieldy use of all the individual combinations of the T, N and M categories and of that the various T.N.M. combinations are presumed to have a similar prognosis, the summary of stage groupings (four categories) shown in Table 3 has been proposed by the Americal Joint Committe.[22)]

Table 3. Summary of Stage Groupings

stage I : T_1, N_0, M_0	Stage IV : T_4, N_1, M_0
Stage II : T_2, N_0, M_0	T_1, N_2, M_0
T_3, N_0, M_0	T_2, N_2, M_0
T_4, N_0, M_0	T_3, N_2, M_0
Stage III : T_1, N_1, M_0	T_4, N_2, M_0
T_2, N_1, M_0	T_1, M_1
T_3, N_1, M_0	T_2, M_1
	T_3, M_1
	T_4, M_1

Norris[20] discussed some of the problems that arise when using this classification and staging system. Most recently there are increasing numbers of observations for laryngeal cancer by means of the T.N.M. system.[23][24][25][26][27] Johnson et al[23] believed this method of review has merit.

Incidence

Clerf et al[28][29] described on that about 4 % of all malignant tumors occur in the larynx, while Scott-Brown et al[22] stated cancer of the larynx accounting for about 2 % of all reported cases of malignant disease.

Laryngeal cancer rarely occurs in young aged peoples. James[30] reported a case with laryngeal cancer in a boy aged 9 1/2 years. Walsh et al[31] reported two young patients (aged 12 and 13 years) with epidermoid carcinoma of the larynx which developed from a beneign lesion of papilloma in the larynx.

In a study of Clerf[29] with an analysis of 250 operative cases of laryngeal cancer, there were 233 men and 17 women, and the majority of the patients were between 50–59 years of age. Eight years later the study, Clerf et al[32] summarized 633 patients with laryngeal cancer operated; there were 39 (6.3 %) women ; and carcinoma more often occured in the decade of 50–59. The youngest was 21 and oldest 87 years. McCall et al[33] observed 8 female among 195 patients with laryngeal cancer, and there was a predominance of its occurrence in the decade of 50–60. In a recent study by Mårtensson et al,[26] 524 patients were men and 54 (9.8 %) women, and a large number of patients was between 50–60 years of age.

The incidence of carcinoma of the larynx in females varies from 3 to 10% according to Friedberg et al.[5]

Clerf et al[28][31] mentioned that while sex and age incidences are of statistical importance, these are of little significance in a study of individual cases. (Fig. 2, 3 and 4)

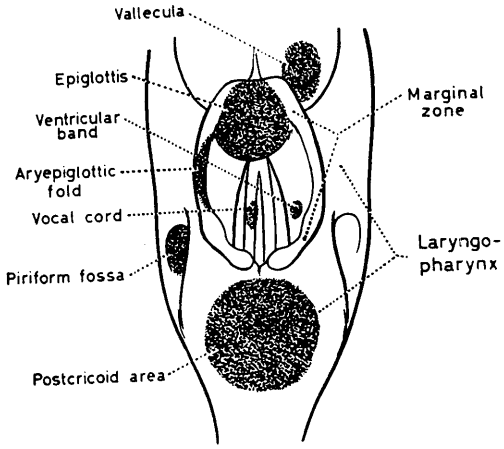

Fig. 2. Posterior view to show common sites of tumor origin ; also the marginal zone between the larynx and laryngopharynx.

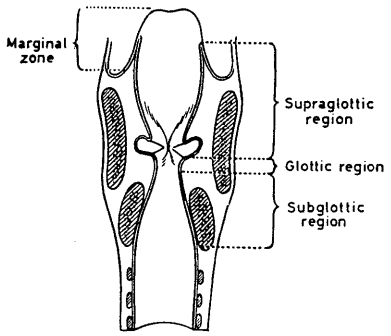

Fig. 3. Coronal section to show the division into laryngeal regions and marginal zone.

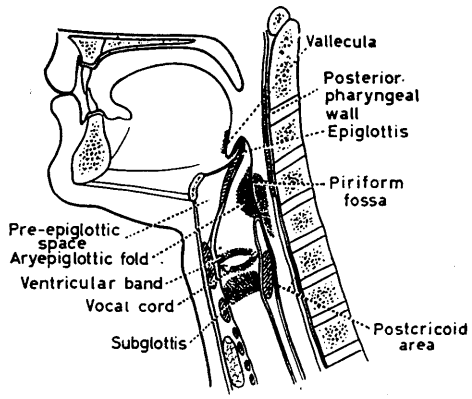

Fig. 4. Sagittal section to show common sites of origin of laryngeal and laryngopharyngeal carcinoma.

Symptoms

The symptoms of laryngeal cancer differ, depending upon the site of the lesion. Hoarseness is an early symptom when tumor develops on the free edge of the vocal cord. In contrast to intrinsic or cordal tumors of the larynx, growths of the extrinsic larynx do not produce early symptoms because small neoplasmas of the extrinsic larynx do not interfere with the voice.

Friedberg et al[5] observed that hoarseness was the only symptom and was present in every 31 patients who had cordal carcinoma, and that the duration of the hoarseness before diagnosis was an average of 7 months. In 18 patients with endolaryngeal carcinoma the symptom of hoarseness was present in each, but 6 patients (or 33 %) also mentioned the sensation of throat discomfort. All of 9 patients with subglottic carcinoma had hoarseness, and 4 of them presented evidence of obstructive dyspnea. They said that subglottic carcinoma does not usually produce symptoms until the lesion has invaded the vocal cord or has caused some narrowing of the airway. The commonest symptom was some form of throat discomfort which was present in 40 (69 %), out of 58 patients with extrinsic or extracordal carcinoma of the larynx. Among this number, 18 complained of actual dysphagia, 7 of localized pain, and 2 of the sensation of a foreign body. Hoarseness was next most frequent symptom, occuring in 35 patients (60 %).

Table 4 shows symptoms and their incidence cited from a report of 149 laryngectomies by McCall et al.[33]

Table 4. Symptoms and their incidence cited from McCall et al[33]

	int.	ext.	total	%
hoarseness	71	82	153	86
alone	33 %	24 %	57 %	86
with other symptoms	7 %	22 %	29 %	
pain	4	29	33	19
hemoptysis	–	9	9	5
sysphagia	2	25	27	5
cough	6	13	19	11
dyspnea	5	13	18	10
palpable mass noted by the patient	–	13	13	7
weight loss noted by the patient	2	10	12	7

int.=intrinsic cancer
ext.=extrinsic cancer

Out of 102 patients with laryngeal cancer observed by Orton,[34] 89 had hoarseness of from six weeks to fifteen years' duration. Local discomfort was noted

in 59 cases. Pain was complained by 45 patients. Another symptoms, dyspnea by 29, stridor or wheeze by 17, difficulty in swallowing by 25, fetor, due to ulceration, by 9, and blood-streaked sputum or saliva by 5, were complained of.

Hoarseness is only an early symptom in carcinoma of the true vocal cord. Many authors,[29)36)] therefore, have had an opinion that hoarseness lasting longer than two weeks demands visualization of the larynx.

Diagnosis

Diagnosis of carcinoma of the larynx depends on the history, examination by both indirect and direct laryngoscopy, examination of the neck, radiographic examination and biopsy with histologic study which makes final diagnosis. General examination including examination of blood and sputum is additional. Cystologic examination of secretion taken directly from the cords may help.

History : Carcinoma of the larynx may often co-exist with syphilis or tuberculosis and may simulate them. Clerf et al,[23)] however, stated that the concomitance of cancer and syphilis of the larynx is rare, and it occured in 4.5 % of 200 cases represented by them. Jackson and Jackson[35)] referred to a number of cases of cancer of the larynx associated with tuberculosis. Against to this report Friedberg et al[5)] reported no co-existence of the two diseases in the same larynx, observing in 166 patients with cancer and in 200 patients with tuberculosis.

Tobacco smoke and heavy drink of alcohol are regarded as etiological agents for laryngeal cancer, therefore careful take of the history concerning these habits must be done. In some instance occupation is important.

Examination by both indirect and direct laryngoscopy : Even though mirror (or indirect) laryngoscopy is the easiest way to make diagnosis of cancer of the larynx, it is not adequate for tumors located in the ventricule, subglottic area and deep in the pyriform sinus. In the subglottic region a lesion may not be seen on indirect laryngoscopy because it is hidden by the overlying edge of the vocal cord. Maloney[37)] described on that an inadequate mirror examination may worse than none at all. Direct laryngoscopy is not only the only way to examine adequately hidden areas of the larynx, but also to obtain any possible additional information of obvious carcinomas diagnosed readily by mirror examination.

The appearance of the lesion vary with the site. It is very rare for a growth to commence on the arytenoids or in the interarytenoid region.[22)] In cordal carcinoma, an irregular, constructive process is seen on one or both vocal cords. The growth usually begins on the anterior half of one cord. It extends across the anterior commissure to the opposite cord or posteriorly to the arytenoid of the same cord. Impaired mobility of the vocal cord is not an early sign since

it is mainly due to either infiltration of the cord or involvement of the nerve supply by the tumor lesion. Notwithstanding impaired mobility is frequently present when first examined and therefore is an important sign. In the Orton's observation,[34] when cancer was diagnosed 30 cases were cords free, 39 cord sluggish and 33 cord fixed.

When carcinoma of the subglottic region begins to infiltrate the submucous tissue and to the vocal cord, limitation of the vocal movement which is mostly a limitation of full abduction together with some sluggishness in adduction may appear.

When a tumor commences in the ventricle a slight fullness of the ventricular band on that side appears in the early stage, and later it becomes to some edema or prolapse of the mucosa of the ventricle. If the ventricular band is pushed outwards it may be seen to be hiding a comparatively large tumor.

In extrinsic lesion, especially epiglottis, the tumor is often fungous and ulcerate.

The pooling of secretions in the pyriform sinus may be the only clue to a lesion of the post-cricoid larynx or cervical esophagus.

Examination of the necck: Nodal meatsitesis from carcinoma of the larynx have long been recognized to occur with high frequency in the extrinsic from and very infrequently or rarely with carcinoma limited to the true cord. Although any node in the neck can be involved, the most common metastasis is high in the neck at the level of the carotid bifurcation. Most of the nodes are under the sternocleidomastoid muscle where they may be easily overlooked unless the neck is palpated carefully.

Ogura et al[38] mentioned that there was a progressive increase in metastatic incidence from glottic, infraglottic, supraglottic and transglottic, 0, 19, 33 and 52 per cent respectively. There are detail studies for laryngeal cancer and neck metastasis.[19][39][40]

Mårtensson et al,[26] observing 578 cases of laryngeal cancer, described on that lymph node metasteses were found in 18.8 % in the supraglottic case, in 4.1 % in the glottic and in 10.8 % in the subglottic cases. The exact statistics is shown by Table 5. Table 6 is made from Spencer's observation,[27] indicating that Stage III and IV include all cases with palpable cervical metastasis which is equivalent to 22.5 % of all laryngeal cancers observed by him. Table 7 is cited from Johnson's et al,[23] pointing out 21 nodal metastases out of 100 laryngeal cancers.

Ogura[19] stated that the size of the local laryngeal lesion was not related to the incidence, or the appearance of the first evident metastesis and therefore the grade of the local lesion was of little help in predicting cervical metastases. This matter is well testfied by Table 5, 6 and 7.

Table 5. Series of Larynx Carcinoma 1940-1959 cited from Martensson et al[26]

	supraglottic	glottic	subglottic
$T_1N_0M_0$	12	186	3
$T_2N_0M_0$	12	71	1
$T_3N_0M_0$	12	190	4
$T_4N_0M_0$	16	36	1
$T_{1-4}N_{1-2}M_0$	12	21	1
total	64	504	10

Table 6. Carcinoma of the Larynx, Clinical Stages made from Spencer's paper[27]

	supraglottic	glottic	subglottic
Stage I	2	27	0
$T_1N_0M_0$ 29			
Stage II	26	22	5
T_2 33			
T_3 14			
T_4 6			
Stage III	6	2	1
T_2N_1 5			
T_3N_1 4			
Stage IV	15	0	0
T_4N_1 9			
$T_4N_1M_1$ 2			
T_2N_2 2			
T_4N_2 1			
T_1N_2 1			
total 106	49	51	6

Table 7. Carcinoma of the Larynx, Clinica Stages cited fron Johnson et al[23]

	patients	percentage
Stage I		31
$T_1N_0M_0$	31	
Stage II		48
$T_2N_0M_0$	15	
$T_3N_0M_0$	25	
$T_4N_0M_0$	8	
Stage III		9
$T_1N_1M_0$	2	
$T_2N_1M_0$	0	
$T_3N_1M_0$	7	
Stage IV		12
$T_4N_1M_0$	1	
$T_1N_2M_0$	0	
$T_2N_2M_0$	0	
$T_3N_2M_0$	1	
$T_4N_2M_0$	10	
T_1M_1	0	
total	100	100

Radioraphic examination : In recent years, the roentgen ray examination has become of increasing value in connection with the diagnosis of laryngeal disease. Routine radiological examination includes lateral and antero-posterior views of the neck, tomographs and the use of contrast media (laryngograms).

Lateral and antero-posterior soft-tissue views of the larynx show the disease outline distinctly, especially demonstrate the presence of a tumor of the epiglottis,

postcricoid or subglottic region. Kelly[47] illustrated the value of x-rays examination of the larynx showing several pictures.

Scott-Brown et al[22] and Maloney[37] explained that tomography (larminography) is of the greatest value, especially in the detection of subglottic and ventricular lesions. However, Ogura et al[38] indicated the disadvantage of tomography that does not clearly demonstrate the detail of certain specific structures under question, e.g., false cord and ventricle with false cord tumors.

The main advantages of contrast laryngography are that tumor masses of the hypopharynx, larynx and trachea can be more accurately defined as to location, size and extent, according to Kelly.[4] Functional impairment can also be demonstrated. Another value is to document objectively the effects of radiation on malignant tumors mainly for radiotherapist. Ogura et al[38] carried out a detail study for laryngogram. In this study they concluded that the laryngogram is necessary for accurate diagnosis of laryngeal cancer, because it can more accurately localize and objectively document the sixe of the cancer than clinical evaluation.

Biopsy : The size of the biopsy specimen removed varies with the site of the lesion. Deweese et al[36] and Maloney[37] stated that in the lesion of the true cord, a smalerl piece of the specimen should be taken because if the patient does not have a malignancy, removal of a large piece of tissue may produe permanent damage to the vocal cord. (Table 8 and 9)

Table 8. Hisiological Grading of Squamous Cell Carcinomas cited from Broders[42]

grades	percentage of cells undifferentiated
1	0 - 25
2	25 - 50
3	50 - 75
4	75 - 100

Table 9. Degree of Malignancy cited from Clerf[29]

	low degree	intermediate	anaplastic
cases of laryngofissure	35	102	12
cases of laryngectomy	12	84	5
total	47	186	17

Biopsy is often misleading. The pathologist can give an opinion only on the tissue submitted to him and not on the entire growth. Therefore, if a representative specimen of tissue is not submitted, the report is misleading. Clerf et al[28] emphasized "an adequate specimen should consist of a portion of the growth including an edge of the normal tissue." Frequently, a malignant lesion is surrounded by inflammatory changes. If a specimens were removed from its surface, they may not contain definitely malignant tissue. So, if the report is negative in spite of the suggestive clinical appearnces, another specimen should be secured.

A danger of facilitating dissemination of the growth due to biopsy is offered. Kelly[41] advised that in certain cases, needle biopsy is preferable, especially when it considered inadvisable to leave a punched-out wound, or open tissue planes to infection or tumor cell implantation. Clerf et al,[28] however, for a number of years have made a special effort in the examination of specimens removed at operations and autopsies after biopsy to determine whether or not there was any evidence of dissemination of the growth following this procedure. Their observations were entirely negative as to the deleterious effects.

To take biopsy specimens should be done after x-ray examinations because the trauma caused by taking the specimens give rise to edema and consequent over-reading of the x-ray pictures.

Pathology

Broders[42] proposed a system of histological grading of squamous cell carcinoma of the lip in 1920, and 5 years later it was applied for the larynx. Table 8 indicates this system. Pathologists, however, were not agreed that an accurate opinion concerning the grade or degree of malignancy can be given on the basis of study of the small specimen submitted for examination.[29] Recently, a modified form of Broders's classification has increasingly been used, which consists of three categoried: "well", "moderately" and "poorly" differentiated.

In 102 cases with laryngeal cancer observed by Orton,[34] intrinsic was 62, subglottic 15 and extrinsic 23 in using Thomson's classification.[14][15] Microscopically, squamous cell carcinoma is 75 %, basal cell carcinoma 3 %, papillary carcinoma 20 % and adenocarcinoma 2 %. He concluded that adenocarcinoma is usually in the ventricle, and in the basal cell type there is apt to be little tendency to recurrence. According to the classification of Broder, the growth in 73 cases was reported by the pathologists as of grade 1 in 27, of grade 2 in 26, of grade 3 in 16 and of grade 4 in 4.

In Clerf's study[29] which consists of two groups, 149 patients performed on laryngofissure and 101 patients on laryngectomy, the degree of malignancy was illustrated on Table 9, and sites of the primary growth on Table 10.

Table 10. Sites of the Primary Growth cited from Clerf[29]

cases of laryngofissure	149
limited to one vocal cord	113
extension across anterior commissure to opposite vocal cord	16
subglottic region	18
arytenoid cartilage	2
cases of laryngectomy	101
epiglottis	
subglottic region	11
postcricoid area	1
interior of larynx (presumably intrinsic)	84

Clerf et al[31] mentioned that practically all primary carcinomas of the vocal cords and epiglottis are of a low or intermediate grade of malignancy, while carcinoma of a ventricular band, arytenoid or subglottic region is more often undifferentiated.

Pietrantoni and Fior[43] reported 570 cases of cancer of the larynx and hypopharynx. All these cases except 48 were proved to suffer from squamous celled carcinoma. The exact data is on Table 11. They stated that basal cell carcinoma of the larynx spreads rapidly, regardless of its macroscopical aspect and shows a less favorable prognosis than the squamous celled type.

Table 11. Histological Types of Tumors cited from pietrantoni et al[43]

	number of cases
squamous cell carcinoma	522
basal cell carcinoma	31
poorly differentiated carcinoma	15
cylindrical cell carcinoma	1
sarcoma	1
total	570

Shaw[44] observed 306 patients with glottic cancer of the larynx and obtained the result that cordal carcinoma showed a relatively high degree of differentiation, 80 % correctly shown by Table 12. Contrastly to this observation, he previously informed an incidence of 29 % moderately differentiated and 15 % poorly differentiated non-cordal and laryng-pharyngeal tumors.

Table 12. Histological Types and Grading of Laryngeal Cancer cited from Shaw[44]

	male	female	total	%
squamous cell carcinoma				
well differentiated	224	19	243	79.5
moderately differentiated	38	3	41	13.4
poorly differentiated	16	3	19	6.2
adenocarcinoma	2		2	0.6
fibrosarcoma	1		1	0.3

In the study by Ogura[19] there were 18 endolaryngeal carcinoma, 13 subglottic carcinoma and 28 extrinsic carcinoma. He summarized that 55 tumors (93%) were characterized by ulceration, fungation and deep infiltration; three were exophytic, papillary structures and infiltration was minimal. Fifty-six tumors (95 %) were of the squamous cell vaiety and three were adenocarcinomas.

From reviewing of many literartures, it is well recognized that 1. laryngeal cancer mainly occurs in the true vocal cord, 2. the great majority of the tumors are squamous cell carcinoma and remainder are composed of basal cell carcinoma and adenocarcinoma and 3. cordal carcinoma shows a relatively high degree of histological differentiation of squamous cell carcinoma.

Multiple primary tumors

Multiple primary tumors have increasingly reported since Billroth[45] first described on it in 1869. He proposed three strict criterias as being essential to the correct diagnosis, which were modified by Warren and Gates to follows: 1. each tumor must be distinct and separate histologically; 2. each tumor must present a definite picture of malignancy; 3. the probability of one tumor's being a metastases of the other must be excluded.

In Shaw's series,[44] there were 23 patients with multiple primary cancers, out of 306 patients with laryngeal cancers.

In the population as a whole, the incidence of multiple primary malignant neoplasms is variously reported as ranging from 0.3 % to 7.8 %.

Metastatic tumors of the larynx

This condition is exceedingly rare as attested by the fact that only 10 cases have been reported.[34][46][47][48][49][50]

Carcinoma in site

The term carcinoma in situ was used by Broder[51] in 1932 to describe an

early preinvasive stage of intraepithelial carcinoma. Carcinoma in situ of the larynx is frequently recognized by biopsy material taken from cases in which the clinical diagnosis of cancer is not apparent. Fischer[52] mannaged 13 cases of carcinoma in situ of the larynx and discussed in detail. Moreover there are many reports[53][54][55][56][57][58] of this condition in the larynx.

Therapy

Carcinoma of the larynx is treated by surgery or irradiation, or both. In the past time irradiation therapy had mainly been used for later inoperable cases. Recently, but it is one of the favorable means for an early stage cancer of the vocal cord preserving his voice, resulting the same cure rate of surgical treatment.

A great number of surgical techniques for treatment of laryngeal cancer have been described. These are follows:

Partial laryngectomy
- laryngofissure — cordectomy
- partial lateral laryngectomy
- partial front-lateral laryngectomy
- epiglottectomy-horizontal laryngectomy
- lateral hemilaryngectomy

Total laryngectomy

Total laryngectomy with simultaneous neck dissection

pietrantoni and Fior[43] employed these techniques and mentioned their indications in detail.

Endolaryngeal eradication: Lillie[59] stated that it is possible to apply adequate eradication by the aid of electric cautery through the medium of suspension laryngoscopy to in situ lesion. Shahrokh et al[60] noted that certain lesions of the tip or the surface of the epiglottis can be cared a similar fashion with suprisingly good results.

Kernan[69] had two cases in which the tumor was completely removed endscopically when tissue was taken for biopsy. In one of his case no further procedure was done without recurrence. However Lynch reported 9 cases of endoscopic removal of a laryngeal carcinoma with 3 recurrences, according to Kernan.[69] Kernan[69] and Jackson et al[70] had same opinion each other that while endoscopic removal is possible it is not to be recommended.

Laryngofissure: Laryngofissure is described in Stedman's Medical Dictionary[61] as follow: operative opening into the larynx, generally through the midline, commonly done for the excision of early carcinoma or correction of laryngostenosis. The early carcinoma of the larynx may define to a lesion with free movable cord, not extending to the anterior commissure, nor posteriorly to the vocal process, and being confined to the vocal edge.

There are many reports[29][62][63][64][65][66][67] concerning laryngofissure used for treatment of selected cases of cordal carcinoma. Reviewing these literatures, five-year survical rates are grossly varying from 59 to 87 per cent.

For reasons of salvaging normal function of the larynx and the relative paucity of true cordal lymphatics, laryngofissure as well as other conservative treatments is chosen as a method of treatment of cordal carcinoma, in spite of that malignant tumor must be widely excised, including the encirclement of the lesion through normal tissue.

McGavran et al[66] offered the strict criteria for the evaluation of laryngofissure as a method for treating intrinsic epidermoid carcinoma (limited to a mobile true vocal cord) of the larynx. These are as follows:

The operation is considered as success if:

1. Laryngofissure was the only definitive therapeutic procedure.
2. The patient is alive five years of more without evidence of persistent carcinoma.
3. The patient died in less than five years, was necropsied and no persistent carcinoma found.
4. The patient died five years or more after treatment without evidence of persistent carcinoma.

It is considered a failure if:

1. Subsequent irradiation therapy or surgery were employed.
2. Persistent carcinoma was demonstrated by biopsy.
3. The patient died of carcinoma of the larynx.
4. The patient died in less than five years without being necropsied.
5. The patient was lost to follow-up.

In their siries of cordal carcinoma performed on laryngofissure, 43 (57 %) out of 79 cases, satisfied the criteria for success, while 34 (43 %) were classified as failtures. The analysis and statistical significance of the pathological data are shown in Table 13. They concluded that the degree of diferentiation of the

Table 13. Correlation of Pathological Findings and Outcome cited from McGavran et al[66]

differentiation	success	failure	total	per cent favorable
(pathologica l findings)				
well	31	11	42	74
moderate and poor	8	15	23	35
in situ car, only	6	1	7	86
tumor at the margin	5	16	21	24
muscle invasion	9	12	21	43

carcinoma, the presence of tumor at the excisional margins, and invasion of the intrinsic muscle are pathological features that are significantly related to the failure of this technique, and that success of laryngofissure is dependent upon careful selection of candidates for the procedure, enbloc removal of the specimen so as to encompass the lesion, and careful pathological examination and interpretation.

Sessions et al[67] exhibited results of laryngofissure in the treatment of carcinoma of the vocal cord, employing the strict criteria of McGavran et al. The results are presented in Table 14. In this series the rate of the success is very high. They defined indications for laryngofissure in the treatment of carcinoma of the vocal cord as follows: 1. Tumor limited to the true vocal cord with no subglottic or supraglottic extension; 2. Fully preserved mobility of the true vocal cord; and, 3. Microscopic diagnosis of carcinoma which is not undifferentiated. In additional description, invasion of the anterior commissure in lesion which involve the true vocal cord only is not felt to be a contraindication to laryngofissure. They compared the results of radiological and surgical treatment of carcinoma of the vocal cord as reported in the literature and found approximate each other closely.

Table 14. Results of Laryngofissure Operation 1938-1963 cited from Sessions et al[67]

	No. of Cases	Per Cent
1. Alive over 5 years without further treatment	19	62
2. Dead under 5 years with autopsy	1	3
3. Dead over 5 years without further treatment	6	20
4. Alive over 5 years with further treatment	2	6
5. Dead under 5 years without autopsy	2	6
6. Dead of carcinoma of the larynx	1	3
7. Lost to follow-up	0	0
8. Alive under 5 years without further therapy	8	–
9. Alive under 5 years with further therapy	1	–
Success	26	84
Failure	5	16
Success	28	90
Failure	3	10

With regard to lesions of the anterior commissure treated by laryngofissure, Putney et al[68] reported a recurrence rate of 44 per cent and considered the location a contraindication to the conservative type of operation.

Laryngofissure is a very favorable method in the treatment of cancer of the vocal cord, preserving the function of the larynx. However it must be required strict definitions for indication of operation.

Hemilaryngectomy : Hemilaryngectomy is usually adequate for a lesion which involved entirely vocal cord with either totally or partialy fixation, and for cases in subglottic cancers, which strictly sited unilateral. However when the lesion crossed the middle or spread to the laryngeal aspect of the arytenoid, or occupied bilateral in the subglottic region, this procedure should not be required.

Hemilaryngectomy was first performed by Billroth in 1875,[45] mostly with the aim of diminishing the high mortality rate due to the total laryngectomy. Futher, the procedure was used for preserving voice and breathing through a normal airway. Pietrantoni and Fior,[45] but, abandoned it on account of the occurence of laryngeal stenosis and reccurrences commonly. They agreed with Tapia who said : "Every time you find a case of tumor whose site and extension would indicate hemilaryngectomy and you will give your patient more chances of survival". Contrastly, Leriux-Robert[71] mentioned that hemilaryngectomy yielded a 70 % five year cure rate in treatment of unilateral subglottic cancers.

Partial fronto-lateral laryngectomy : Tumor of the anterior two thirds of one vocal cord with involvement of the anterior commissure, crossing slightly the midline, or else tumor arising on the anterior commissure and spreading to the anterior third of one vocal cord is indicated for this procedure. In this lesion yet the vocal cord is perfectly mobile. Norris[72] used "extended fronto-lateral laryngectomy" for lesions of somewhat greater extent than the tumor above mentioned, such as those showing, a. posterior extension to or beyond the tip of the vocal process, but not into the posterior commissure ; b. beginning impairment of motility without actual fixation of the cord ; c. limited and superficial extension to ventricle or margin of ventricular band ; or d. subglottic extension amounting to no more than a few millimeters.

This procedure has less frequently been applied.

Epiglottectomy (partial horizontal laryngectomy) : This method is applied for tumors of the laryngeal surface of the epiglottis with or without invasion of preepiglottic space and partial spreading to the ventricular bands.

Ogura[73] treated 15 patients with carcinoma of the epiglottis by supraglottic subtotal laryngectomy and radical neck dissection. The patients treated could have not only a good voice and a normal airway, but also were able to swallow normally without the protective function of the epiglottis, aryepiglottic folds or false cords.

Total laryngectomy : Total laryngectomy is performed more often than partial laryngectomy and indicated in patients with for advanced lesions.

In the history of total laryngectomy[22] Watson belongs to the honour of first performing this method. But on that occasion the operation was performed for

syphilis. It was Billroth who first removed the larynx for cancer in 1873.

Ogura[8] explained in detail on the histological development of laryngectomy.

According to Orton,[74] the indications for laryngectomy are as follows:

1. When the growth has exteoded to the anterior commissure or has extended backwards to the arytenoid.
2. When the epiglottis is involved below the level of the hypoglottic ligament.
3. When the growth has crossed to the opposite side, and there is subglottic extension.
4. The growth springing from the ventricle or ventricular fold.
5. The growth has invaded the thyroid cartilage or cricoi-thyroid membrane.
6. In extrinsic carcinoma of the larynx.
7. Defimite fixation of one or both vocal cords.
8. The growth is subglottic in origin.
9. In a recurrence following a laryngofissure operation.
10. Where the larynx has been subjected to unsuccessful irradiation in selected cases.

There are two kinds of the technique in laryngectomy, narrowfield laryngectomy and wide-field type of extripation. In more recent years the wide-field laryngectomy has much frequently utilized. The latter consists of removing the hyoid bone, epiglottis and tissues about the pre-epiglottic space, larynx, strap muscles, the upper two or three tracheal rings, and the lobe of the thyroid on the side of the lesion if it is one-sided.

In the series of Clerf et al,[32] of the group of 176 cases treated by laryngectomy that could be treated five or more years after operation, there are 81 living and free from recurrences (58.7 %). The 176 cases were accounted for as follows: well and free from recurrence after five year, 81; postoperative deaths, 9; intercurrent deaths within five years unrelated to carcinoma of larynx, 23; unable to trace 6,; recurfences, 57.

The disadvantages of total laryngectomy are that if involves the loss of a laryngeal voice, interruption of the natural airways with substilution of a permanent tracheal stoma in the neck, and definite limitations on some forms of physical activity such as swimming and heavy manual work. Therefore, many patients who must have total laryngectomy spare the loss of voice.

After total laryngectomy there is a permanent opening into the trachea through the neck. The patient can breathe through the nose, so there in no sense of smell. However, there is no tendency in suffering from pneumonia or other lower respiratory disease.

Knight[75] discussed on crust formation in the tracheobronchial tree of laryngectomized patient. Low humidity causes the crust formation.

Associated radical neck dissection : Combined laryngectomy and radical neck dissection is done when the laryngeal lesion is advanced, lymph nodes are palpable

on the neck and the lesion is an extra cordal of high degree (histological grading), even if no nodes are palpable, because of high tendency toward the metastesis to the regional lymph nodes.

The term "prophylactic or elective" is used to modify the term radical neck dissection for an operation performed in the absence of palpable nodes, and therapeutic neck dissection refers to surgery for clinically positive nodes.[18)19)]

The value of radical neck dissection for metastatic squamous cell carcinoma was first described by Crile[76)] in 1906. In 1942, sylvester-Begnis, citing from Ogura,[18)] advocated the use of radical neck dissection and laryngectomy as a one-stage procedure. Clerf et al[32)] mentioned that laryngectomy and prophylactic radical neck dissection were indicated in cases with questionable nodal involvement.

In the kuhn[39)] et al siries of 602 cases of squamous cell carcinoma of the larynx, among 31 of histological grade four, 70 % metastasized; and among 183 of grade three, 47 % metastasized.

Ogura et al[18)] reported that microscopically positive nodes were found in 7 out of 18 prophylactic neck dissections (38,8 %), and 6 of the 15 occured with subglottic and endolaryngeal carcinoma (40 %). They suggested that the cure rate may be improved if prophylactic neck dissections were done routinely in extensive laryngeal carcinomas. They were of opinion that dividing the operation into two stages will cut involved lymphatic, which is contrary to sound surgical principles, and therefore, the two-stage operation has given poor results.

The disadvantages of the combined operation are that postoperative wound infection and pharyngeal fistula occur more often than only wide-field laryngectomy is carried out.

Radiation therapy:

At the present time it is generally acknowledged that for early carcinoma limited to one true cord (without fixation), the results by irradiation are good and almost approximate those of surgery. However, irradiation therapy does not least good in patients with far-advanced carcinoma, subglottic extension, and neck metastasis.

The advantage of the irradiation therapy is to leave the patient with a better voice than results from an operation, even partial laryngectomy.

Methods of this treatment are mainly devided into two, intersititial and external irradiations. The former is by radium and the latter by x-ray, Cobalt-60, or beta-tron.

Intersititial irradiation: Radium therapy for a tumor of the larynx is well known as the Finizi-Harmer operation. This method is that a window is made in the thyroid ala and radium needles are arranged vertically by inserting their points and eyes between the window margins and the intact inner perichondondrium.[77)] It is possible to deliver a high dose of about I0,000 r. to the tumor without

damaging the skin.

Brown et al[77] treated 106 cases of vocal cord cancer by this method. Eighty-one patients, or 76.4 %, out of these 106 cases survived for a period of at least 5 years, leaving 25 patients who died. They concluded that the commonest cause of failure is shown to be faulty judgement in selection of case, however the Finzi-Harmer operation played an important part in the evolution of the treatment of vocal cord cancer.

External irradiation: Caulk[25] observed 202 patients with laryngeal cancer who were treated by radiation, using TNM system. Among them there were 28 cases which underwent subsequent surgery for uncontrolled disease. Regardless of the anatomic site of origin, Stage III and IV groups were failure to cure. In 5 years survival rate, Stage I, $T_1N_0M_0$ was 81.3 %, Stage II, $T_2N_0M_0$ 53.0 %, $T_3N_0M_0$ 54.6 %, and $T_4N_0M_0$ 40.0 %.

Wang et al[78][79] managed 276 patients with cancer of the larynx primarily by radiation therapy from 1935 to 1957. Five-year survivals with 89 % in Stage I, 82 % in Stage II, 49 % in Stage III, and 13 % in Stage IV were accomplished by radiation therapy. Of 14 patients in whom radiation therapy failed to control disease, 12 were subsequently rescued successfully by laryngectomy.

Liegner et al[24] reported 48 cases of laryngeal and laryngopharyngeal cancer treated by Cobalt-60. Five-year survivals were 75 % in the glottic group, 60 % in the epiglottic group, and 40 % in the laryngopharyngeal group. Cases with nodal metastasis were almost failed to cure. They mentioned that the results of Cobalt-60 therapy in all groups were achieved with minimal immediate local reactions and significant late complications.

Radionecrosis is one of the disadvantages of radiation therapy Marchetta et al[80] found that radionecrosis resulted in 10 % of 118 cases of the intrinsic cancer of the larynx treated by irradiation, and that death usually resulted unless the necrotic tissue were excised. It generally is acknowledged that healing is likely to be delayed after surgery which follows a radical course of radiation therapy, and also that infection and fistulization are more frequent than if radiation therapy had not been given.

Fletcher[81] stated that these complications are less if Cobalt-60 has been used.

Taking it as a whole, for carly carcinoma limited to one true vocal cord (Stage I), the results by irradiation are good and almost approximate those of surgery, however it does least good in patients with far-advanced carcinoma, subglottic extensions, and neck metastesis.

Combined therapy of surgery and irradiation : The use of combined treatment in head and neck cancars was first recommended by Leroux-Robert[71] in 1956.

There are three methods in combined therapy. These are preoperative irradiation, postoperative irradiation and so-called "sandwich" method.

Combined therapy is usually used for advanced carcinoma.

Reed[82] described on "preoperative irradiation in laryngeal carcinoma". From his paper, the principle of preoperative irradiation is basically to destroy the radio-sensitive peripheral cells of the tumor so that the relatively radio-resistant central cells may be removed by surgery.

In regard to that the amount of irradiation dosage and the time interval between x-ray therapy and surgery, there are two thoughts. The first advocates the use of low dosage radiotherapy in a short period of time, ie, 2000 to 3000 rads in one to two weeks' time. The other advocates the use of full cancerocidal dosage of 5500 to 6000 rads with a waiting period of four to six weeks before surgery.

Moreover, there are several publications concerning combined therapy of surgery and irradiation.[83][84][85][86][87]

Reed[82] is of opinions that early stage carcinoma of the true vocal cord without limitation of the cordal movement is best treated by radiation alone. Statistically the cure rates of radiation and cordectomy are approximately equal, and the resultant voice is better with radiotherapy. Stage II or more advanced lesions of the endolarynx with loss of cord mobility are better cured by surgery consisting of one of the many subtotal or total laryngectomy, but preoperative erradiation would further enhance the cure rate. More advanced lesions involving large areas of the endolarynx and those involving other areas of the hypopharynx, including lesions of the pyriform sinu, postcricoid area, and large lesions of the epiglottis and aryepiglottic folds are treated by combined therapy of surgery and radiation with the greatest advantages.

Ogura[88] indicates methods of treatment for various regions and sites and stages of laryngeal cancers, as shown by Table 15.

Table 15. Methods of Treatment for Carcinoma of the Larynx cited from Ogura[88]

Location	method
Intrinsic (glottic, Stage I)	Irradiation Laryngofissure (2nd choice) Hemilaryngectomy
Endolaryngeal (Subglottic)	Laryngectomy, neck dissection
Extrinsic (with cordal fixation, arytenoid involvement)	
Postcricoid or pyriform sinus extension into esophagus	Laryngopharyngoesophagectomy and neck dissection
Epiglottic without cordal involvement	Supraglottic subtotal laryngectomy, neck dissection
Epiglottic without cordal involvement, base of tongue invaded	Extended supraglottic subtotal laryngectomy, neck dissection
Pyriform sinus without cordal-arytenoid involvement	Transhyoid partial pharyngectomy and neck dissection

Prognosis

Carcinoma of the larynx is more curable lesion than that of others.

Carcinoma of the larynx arising from the true vocal cords produces a very early symptom-hoarseness. If the patient consults to an otolaryngologist immediately becoming hoarse, the diagnosis can be made early, and the prognosis is then excellent, not lossing his voice.

But carcinoma arising from another parts of the larynx, especially aryepiglottic fold, subglottic region and pyriform sinus, take a latent course for considerable times. Therefore, when the lesion is explored it is in Stage III or more late. The prognosis is then worse with loss of his voice.

Summary

Many problems of carcinoma of the larynx are disccussed from reviewing literatures.

REFERENCES

1) Wynder, E. L., Bross, I. J., and Day, E.: Epidermiological approach to the etiology of cancer of the larynx. *J.A.M.A.* **160**; 1384-1391 (April) 1956.
2) Dunn, W. I. and Dykstra, C. L.: Tobacco habits in carcinoma of the upper respiratory tract. *Arch. Otolaryng.*, **86**: 105-107 (July) 1967.
3) Jackson, C., and Jackson, C.L.: *The larynx and its disease.* Philadelphia, W.B. Saunders Company 1937 cit. from 4)
4) Wallner, L.J.: *Smoker's larynx*, **64**: 259-270 (April) 1954.
5) Friedberg, S. A., and Wallner, L. J.: Selected problems in the diagnosis of laryngeal carcinoma. *Arch. Otolaryng.*, **58**: 521-535 (Nov.) 1963.
6) Clerf, L.H., Putney, F.J., and O'Keefe, J.J.: Carcinoma of the Larynx. *Laryngoscope*, **58**: 632-641 (July) 1948.
7) Muir, C.S.: The incidence of laryngeal cancer in Singapole. *J. Laryng. and Otolog.*, **79**: 203-213 (Mar.) 1965.
8) Sanghvi, L.D., Rao, K.C.M. and Khanolkar: Smoking and chewing of of tobacco in relation to cancer of the upper alimentary tract. *Brit. Med. J.*, **1**: 1111-1114 (May) 1955.
9) Waldenström, J.: The incidence of "Iron Deficiency" (Sideropenia) in some rural and urban population. *Acta Med. Scandinav.*, Supp. **170**: 252, 1946.
10) Jacobsson, F.: Carcinoma of the hypopharynx. *Acta Radiol.*, **35**: 1, 1951. 9) and10) Cit. from1)
11) Piquet, J.: Le Cancer de la Corde Vocale. 1958 Paries cit. from7).
12) Sato, T., Utsumi, S., Kajikawa, K. and Ikeda, H.: A case of cancer of the larynx found in mustard gas poisoning. J. oto-Rhino-Laryngolog. Soc. Jap., **70**: 1773-1778 (Nov.) 1967.
13) Krishaber: *Gaz Hebd. de Med et de Chirurg.*, 1879, lVL, 33, 518 cit. from
14) Thomson, St.C.: Intrinsic cancer of the larynx. *Jour. Laryngol. and Otol.*, **36**: 462-463 (Oct.) 1921.
15) Thomson, St.C.: Subglottic cancer of the larynx. *Jour. Laryngol. and Otol.*, **52**: 802-816, 1937.
16) Semon, F.: Diagnosis and treatment of laryngeal cancer. *Brit. Med. Jour.*, **1**: 214-248 (Feb.) 1907.
17) Walsh, T.E.: The classification of carcinoma of the larynx. *Laryngoscope*, **57**: 414-418 (June) 1947.
18) Ogura, J. H. and Bello, J.A.: Laryngectomy and radical neck dissection for carcinoma of the larynx. *Laryngoscope*, **62**: 1-52 (Jan.) 1952.

19) Ogura, J.H.: Surgical pathology of the larynx. *Laryngoscope*, **65**: 867-926 (Oct.) 1955.
20) Norris, C.M.: Problem in classification and staging of cancer of the larynx. *Ann. Otol. Rhinol. and Laryngol.*, **72**: 83-96 (March) 1963.
21) u.I.C.C. (Union Internationale Contre le cancer) (1963) Clinical stage Classification and Presentation of Results. Malignant Tumors of the Buccal Cavity (including the lip) the Pharynx and the Larynx. Geneva.
22) Scott-Brown, W.G., Ballantyne, J. and Groves, J.: *Disease of the ear, nose and throat*, Volume 1, 1965 Butterworths, London.
23) Johnson, N.E. and Sisson, G.A.: Carcinoma of the larynx---review of 100 cases---. *Laryngoscope*, **74**: 710-722 (May) 1964.
24) Liegner, L.M. and McCuaig, D.: Laryngeal cancer--primary treatment with Cobalt 60 in a general hospital. *Radiology*, **84**: 718-725 (April) 1965.
25) Caulk, R.M.: End results of radiotherapy in laryngeal cancer based upon clinical staging by the T.N.M. system. *Amer. J.* Roent., **96**: 588-592 (Mar.) 1966.
26) Martensson, B., Fluur, E., and Jacobsson, F.: Aspects on treatment of cancer of the larynx. *Ann. Otol. Rhinol. and Laryngol.*, **76**: 313-329 (June) 1967.
27) Spencer, J.T.: Cancer of the larynx-- end results report of 106 cases using the clinical staging system. *Laryngoscope*, **77**: 962-1002 (June) 1967.
28) Clerf, L.H. and Crawford, B.L.: Carcinoma of the larynx--clinical and pathological aspects. *Arch. Otolaryng.*, **16**: 676-689 (Nov.) 1932.
29) clerf, L.H.: Cancer of the larynx--an analysis of two hundred and fifty operative cases. *Arch. Otolaryng.*, 32: 484-498 (Sept.) 1940.
30) James, C.: Carcinoma of the larynx in a boy aged 9 1/2 years. *J. Laryngol. and. Otol.*, **67**: 433-437 (July.) 1953.
31) Walsh, T.E. and Beamer, P.R.: Epidermoid carcinoma of the larynx occuring in two children with papilloma of the larynx. *Laryngoscope.*, **60**: 1110-1128 (Nov.) 1950.
32) Clerf, L.H., Putney, F.J., and O'keefe, J.J.: Carcinoma of the larynx. *Laryngoscope*, **58**: 632-641 (July) 1948.
33) McCall, J.w. and Fisher, W.R.: Carcinoma of the Larynx— a report of 194 cases with 149 laryngectomies—. *Laryngoscope*, **62**: 475-485 (May) 1952.
34) Orton, H.B.: Cancer of the larynx — immediate and ultimate results of opration in one hundred and two cases. *Arch. Otolaryng.*, **28**: 151-192 (Aug.) 1938.
35) Jackson, and Jackson: Bronchoesophagology 1937, W.B. Saunders Company, Philadelphia.
36) Deweese, D.D. and Saunders, W.H.: *Textbook of Otolaryngology*, 1960, The C.V. Mosby C., St Louis.
37) Maloney, W.H.: Pitfalls in the diagnosis of cancer of the larynx, *Laryngoscope*, **70**: 774-779 (June) 1960.

38) Ogura, J.H., Powers, W.E., Holtz, S., McGavran, B.E. and Voorhees, R.: Laryngograms: Their value in the diagnosis and treatment of laryngeal lesion. A study based on clinical, radiographic and pathologic findings on 99 patients with cancer of the larynx. *Laryngoscope*, **70**: 780-809 (June) 1960.
39) Kuhn, A. J., Devine, K. D. and McDonald, J. R.: Cervical metastasis from squamous cell carcinoma of larynx and laryngopharynx. *Laryngoscope*, 67: 169-190 (Mar.) 1957.
40) MacGavran, M. H., Baner, W. L. and ogura, J. H.: The incidence of cervical lymph node metastasis from epidermoid carcinoma of the larynx and their relationship to certain characteristics of the primary tumor. A study based on the clinical and pathological findings for 96 patients treated by primary en bloc laryngectomy and radical neck dissection. *Cancer*, **14**: 55-66 (Jan.—Feb) 1961.
41) Kelly, H.D.B.: The diagnosis of laryngeal neoplasm, *Jour. of Laryng. Otol.*, **81**: 375-384 (April) 1967.
42) Broders, A. C.: Squamous cell carcinoma of the lip. *J.A.M.A.*, **74**: 656-664 (March) 1920.
43) Pietrantoni, L. and Fior, R.: Clinical and surgical problem of cancer of the larynx and pharynx—A review of 570 consecutive cases operated on in the Ear, Nose and Throat Clinic of the University of Milan between 1948 and 1954 with special regard to the problem of metastasis. *Acta-Otolaryng.*, (Stockh.) Supp. **142**: 1-61, 1958.
44) Shaw, H. J.: Glottic cancer of the larynx—1947-1956, *Jour. Laryng. and Otol.*, **79**: 1-14 (Jan.) 1965.
45) Billroth, T: cited from Heiner, E.R.: multiple primary tumors of the larynx—A case report—, *Laryngoscope*, 77: 1849-1855 (Oct.) 1967.
46) Turner, A. L.: Metastatic malignant tumor of the larynx secondary to adenocarcinoma of the right kedney, *Jour. Laryngol. and Otol.*, **39**: 181-194 (sept.) 1924.
47) Oppikoder, E: Metastesis of renal hypernephroma in upper respiratory tract and ear, *Arch. f. Ohren-Nases-u. Kehlkoph.*, **129**: 271-292 (Ang.) 18, 1932.
48) Maxwell, J. H.: Metastatic hypernephroma to the larynx, *Univ. Hosp. Med. Bull.*, Ann Arbor, Mich., (April) 1942.
47) and 48) cited from 50)
49) Ellis, M. and winston, P.: Secondary carcinoma of the larynx, *Jour. Laryngol. and Otol.*, **71**: 16 (Jan.) 1957.
50) Fields, J. A.: *Renal carcinoma metastasis to the larynx*, **76**: 99-101 (Jan.) 1966.
51) Broders, A.C.: Carcinoma-in-situ contrasted with beneign penetrating epithelium., *J.A.M.A.*, **99**: 1670-1674 (Nov.) 1932.
52) Fischer, H.R.: Carcinoma-insitu of the larynx, *Ann. Otol. Rhinol. and Laryngol.*, **62**: 358-370 (June) 1953.

53) Votaw, R.: carcinoma in otolaryngology, *Laryngoscope*, **62**: 973-997 (Sept.) 1952.
54) Clerf, L.H.: Cancer of the larynx, Report of unusual case, *Ann. Otol., Rhinol. and Laryngol.*, **53**: 335-338 (June.) 1944.
55) Snitman, M.F.: Carcinoma of the larynx: Significance of histopathologic study of serial section: Preliminary report, *Arch. Otolaryng.*, **42**: 178-185 (Sept.) 1945.
56) Brunner, H.: Superficial epidermoid carcinoma of the larynx, *Arch. Otolaryng.*, 51: 49-64 (Jan.) 1950.
57) Gordon, R.G.: Keratosis of the larynx. Report of a case with underlying carcinoma-in-situ, *Laryngoscope*, 60: 1201-1209 (Dec.) 1950.
58) Altman, F., Ginsberg, I. and Stout, A.P.: Intraepithelial carcinoma (cancer-in-situ) of the larynx, *Arch. Otolaryng.*, **56**: 121-133 (Aug.) 1952.
59) Lillie, J.C.: Cancer of the larynx. *Texas State Jour. of Med.*, **59**: 694-700 (July) 1963.
60) Shahrokh, D.k. et al.: cit. from 59)
61) *Stedman's Medical Dictionary*: Twenty-First Edition. The williams and wilkins Company, Asian Edition: Maruzen company Limited, Tokyo, 1966.
62) Jackson, C.L.: Laryngofissure for cancer of the larynx: Observations based on series of 50 consecutive cases, *Arch. Otolaryng.*, **33**: 520-535 (April) 1941.
63) Schall, L.A.: Carcinoma of the larynx, *New England J. Med.*, **229**: 574-576 (Oct.) 1943.
64) Lejeune, F.E. and Lynch, M.G.: Value of laryngofissure operation, *Ann. Otol. Rhinol. and Laryngol.*, **64**: 256-262 (March) 1955.
65) Schall, L.A.: Symposium; Carcinoma of the larynx IV—Cancer of the larynx. Five-year results, *Laryngoscope* **61**: 517-522 (June) 1951.
66) McGavran, M.H., Spjut, H.J. and Ogura, J.H.: Laryngofissure in the treatment of the laryngeal carcinoma—A critical analysis of success and failure, *Laryngoscope*, **69**: 44-53 (Jan.)
67) Sessions, D.G., Maness, G.M. and McSwain, B.: Laryngofissure in the treatment of carcinoma of the vocal cord: A report of forty cases and a review of the literature, *Laryngoscope*, **75**: 490-502 (March) 1965.
68) Putney, F.J. and Vicens, E.A.: Surgical treatment of carcinoma of the anterior commissure of the larynx, *Laryngoscope*, **66**: 1041-1048 (Aug.) 1956.
69) Kernan, J.D.: A critique of the treatment of laryngeal cancer, *Laryngoscope*, **48**: 295-301 (May) 1938.
70) Jackson, C. and Jackson, C.L.: Cancer of the Larynx, *J.A.M.A.*, **111**: 1986-1993 (Nov.) 1938.
71) Leroux-Robert, J.: Indications for radical surgery, partial surgery, radiotherapy and combined surgery and radiotherapy for cancer of the larynx and pharynx, *Ann. Otol. Rhinol.*

and Laryng., **65**; 137-153 (March) 1956.
72) Norris, C.M.: Technique of extended front-larteral partial laryngectomy, *Laryngoscope*, **68**: 1240-1250 (July) 1958.
73) Ogura, J.H.: Supraglottic subtotal laryngectomy and neck dissection—One stage operation for carcinoma of the epiglottis, *Laryngoscope*, 68: 938-1001 (June) 1958.
74) Prton. H.B.: Symposium: Carcinoma of the larynx. 11—Treatment of extensive carcinoma of the larynx. *Laryngoscope*, **61**: 496-510 (June) 1951.
75) Knight, J.S.: Post-laryngectomy care in the middle Western United States, *Laryngoscope*, **77**: 763-770 (May) 1967.
76) Crile, G.: Excision of cancer of head and neck, J.A.M.A. 1780-1786 (Dec.) 1906.
77) Brown, B. and Lambert, V.: The place of interstitial radium in the treatment of cancer of the larynx. *J. Laryng. and Otol.*, **77**: 279-289 (April) 1963.
78) Wang, C.C. and Schultz, M.D.: Treatment of cancer of the larynx by irradiation, *Ann. Otol. Rhin. Laryng.*, **72**: 637-646 (Sept.) 1953.
79) Wang, C.C. and Schultz, M.D.: Cancer of the larynx—Its management by radiation therapy—*Radiology*, **80**: 963-972 (June) 1963.
80) Marchetta, F.C., Maxwell, W.T., Riegerr, H.C., and Schofinger, R.: Carcinoma of intrinsic laryns, *Surg. Gynec. Obstet.*, **104**: 401-406 (April) 1957.
81) Fletcher, G.H.: Present status of Cobalt-60 therapy in management of the cancer patient, *J.A.M.A.*, **164**: 244-248 (May) 1957.
82) Reed, F.G.: Preoperative irradiation in laryngeal carcinoma, *Arch. Otolaryng.*, **86**: 318-325 (Sept.) 1967.
83) Powers, W.E. and Ogura, J.H.: Preoperative irradiation in head and neck cancer surgery, *Arch. Otolaryng.*, **81**: 153-158 (Feb.) 1965.
84) Hudson, W.R. and Cavanaugh, P.J.: Combined surgical and radiation management of carcinoma of the laryngopharynx. *Laryngoscope*, **75**: 1123-1138 (July) 1965.
85) Goldman, J.L., sidney M. Silverstine, Henry D. Rosin, Robert V. Cheren, and Frederick G. Zak.: Combined radiation and surgical therapy for cancer of the larynx and laryngopharynx II, *Laryngoscope*, **74**: 1111-1134 (Aug.) 1964.
86) Skolnik, E.M., Tenta, L.T., Comito, J.N., and Jerome, D.L.: Preoperative radiation in head and neck cancer; preliminary report, *Ann. Otol., Rhinol., and Laryng.*, **75**: 336-355 (June) 1966.
87) Goldman, J.L., Cheren, R.V., Zak, F.G., and Gunsberg, M.J.: Histopathology of larynges and radical neck specimens; In a combined radiation and surgery program for advanced carcinoma of the larynx and laryngopharynx. *Ann. Otol. Rhinol. and Laryng.*, **75**: 313-335 (June) 1966.

88) Ogura, J.H.: Cancer of larynx, pharynx, and upper vercival esophagus—Five-year results of laryngectomy and radical neck dissection for laryngeal cancer. *Arch. Otolaryng.*, **72**: 66-72 (July) 1960.