EARLY (T1) LARYNGEAL CARCINOMA

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WORK ON THIS DISSERTATION WAS DONE IN THE INSTITUTE OF OTORHINOLARYNGOLOGY (HEAD: PROF. DR. W.F.B. BRINKMAN) AND INSTITUTE OF RADIOTHERAPY (HEAD: PROF. I. KAZEM) OF THE UNIVERSITY OF NIJMEGEN- THE NETHERLANDS. IT IS A PART FULFILMENT FOR THE AWARD OF THE DEGREE OF MSC. OF THE UNIVERSITY OF DAR ES SALAAM- TANZANIA.

SUPERVISOR: PROF. DR. PAUL VAN DEN BROEK.

Dedicated to my beloved parents,
my wife Irene and children Joachim,
Victor, Flavia and Msafiri.

CONTENTS.

EARLY LARYNGEAL CANCER.

1.00.HISTORICAL NOTES.

As early as 100AD (1) laryngeal carcinoma had been recognized as a medical entity. It is reckoned that tracheostomy had been done as early as 90 BC by Aesklapiades (2) but the indication was probably laryngeal obstruction due to diphtheria and not laryngeal cancer. Between 100AD and 17th century, not much was heard about laryngeal carcinoma mainly due to lack of diagnostic endoscopic facilities. Boerhave in 1668 and Morgagni in 1723 described the cause of death in autopsy material as being tumours of the larynx and pharynx. Appreciably, antemortem diagnosis of laryngeal tumours was not possible because there were no aids to visualize the larynx.
More knowledge regarding laryngeal cancer was gained with developments in endoscopic instruments. Bozzini (3) in 1804, developed specula for examining body cavities but these were not universally accepted. Senn, in 1827, and Babington in 1829 did make attemps to visualize the larynx but in vain. It was Garcia, a singing master of Spain and London, who, using a dental mirror with a long stem and a hand mirror, visualized his own vocal cords. Although his report was received with reluctance by the Royal Society of London in 1854, Garcia has been deservingly accorded the title of "father of Laryngology". The task was accomplished by Czermak who succeeded in implementing Garcia's idea by using the laryngeal mirrors passed to him by the Viennese physician, Türck.

In fact TUrck failed to use the laryngeal mirrors !.Czermak, apart from substituting artificial light for sunlight, developed the head mirror for the reflection of light rays. Shortly after indirect laryngoscopy was widely accepted, Kirstein (4) in 1895 described his experience with von Mikulicz's oesophagoscope when he discovered that the vocal cords were well exposed and realized that it was feasible to operate through the instrument.

The credit for developing peroral endoscopy is due to Jackson, an American physician from Philadelphia, in 1905. He designed not only laryngoscopes but also oesophagoscopes and bronchoscopes which were used for direct visualization of the upper aerodigestive tracts; similar or modified designs of Jackson's endoscopes are still in use todate.

With endoscopes readily available, laryngeal cancer diagnosis antemortem was no longer difficult. However, discrepancies did arise regarding whether what appeared as cancer clinically was true or not. Histological confirmation of a cancerous lesion was vital because the only available therapy then was laryngectomy. A documented example relates to the illness of the Crown Prince Friederich of Germany (5) who, in the spring of 1887, developed persistent hoarseness of voice. His attending physician noted laryngeal polyps which, on resisting repeated cauterization, necessitated a second opinion from von Bergmann of Berlin. Basing his judgement on the clinical features alone, von Bergmann recommended surgical intervention. He had, by this time, done seven laryngectomies but the average survival period for the patients was 9 months only. Probably it was on this premise that the Crown Princess Victoria, daughter of Englands Queen,

requested additional medical consultation and Mackenzie, one of England's leading laryngologists, was called to Germany. Unimpressed by the clinical diagnosis, Mackenzie recommended biopsy, which he himself took and submitted the material for examination by the eminent Professor Virchow. Virchow found no cancer cells in the biopsy material, a finding confirmed by London pathologists as well. Surgery was witheld but unfortunately in 1888, Friedrich died and the laryngeal cancer was confirmed at autopsy. While this arose a lot of controversy within the medical and political spheres, it will be appreciated that even todate inadequate or unrepresentative biopsy is reported histologically negative necessitating a rebiopsy. We still abide by Mackenzie's principle of histological confirmation of what appears clinically malignant before the appropriate therapy can be decided upon.

Laryngeal surgery has been practised for centuries. It is possible that the first laryngectomy was accidentally done at suicide attempts but escaped documentation (7) (8) (9) (10). Schuessler, in 1844, reckons a patient who was brought to him with a paper bag that contained his larynx, part of the pharynx and some tracheal rings. This patient survived. Therapeutic laryngeal procedures date back to 1778, when Pelletan is reported to have split a patient's larynx as an emmergency measure to remove a piece of meat wich had impacted. According to Durham (6) thyrotomy was suggested by Desault in the 18th century. In 1844, Ehrmann removed a laryngeal polyp from a 33 year old woman by performing tracheostomy followed two days later by a laryngofissure. Bück (11) in 1851, opened the larynx to remove what he considered to be a laryngeal polyp,

but authorities later believed it could have been squamous cell carcinoma. Watson (12) performed the first total laryngectomy in 1868 for Syphilis. Bilroth (1) performed the first laryngectomy for cancer in 1973. By 1881 laryngectomy was well standardized for cancer and the desire to improve its details and define its indications was overwhelming(13). However the early experiences of this operation were discouraging. The morbidity and mortality rates were so high that the procedure was at risk of being abandoned (14).

Glück and Leller (15) described a two stage operation developed from experiments on dogs in which the trachea was first cut and the distal end fastened to the skin, the larynx beeing removed 4 days later. By 1900, the operative mortality had improved to 91.5%. With improved post operative care and better selection of cases, laryngectomy was becoming better accepted. The nasogastric feeding tube was introduced by MacKenty and readily accepted by other surgeons. In the 1940's endotracheal intubation anaesthesia was introduced and antibiotics became available. These technical and therapeutic developments made total laryngectomy widely acceptable and was indicated in patients with laryngeal cancer that was too extensive for laryngofissure but not too advanced for surgical intervention.

Since then, modifications such as periosteal laryngectomy (17) narrow field laryngectomy (18) and wide field laryngectomy (19) have been described for early and advanced laryngeal cancer respectively. Supraglottic laryngectomy, first introduced by Alonso in 1942, initially met with considerable resistance among laryngologists and head and neck surgeons,

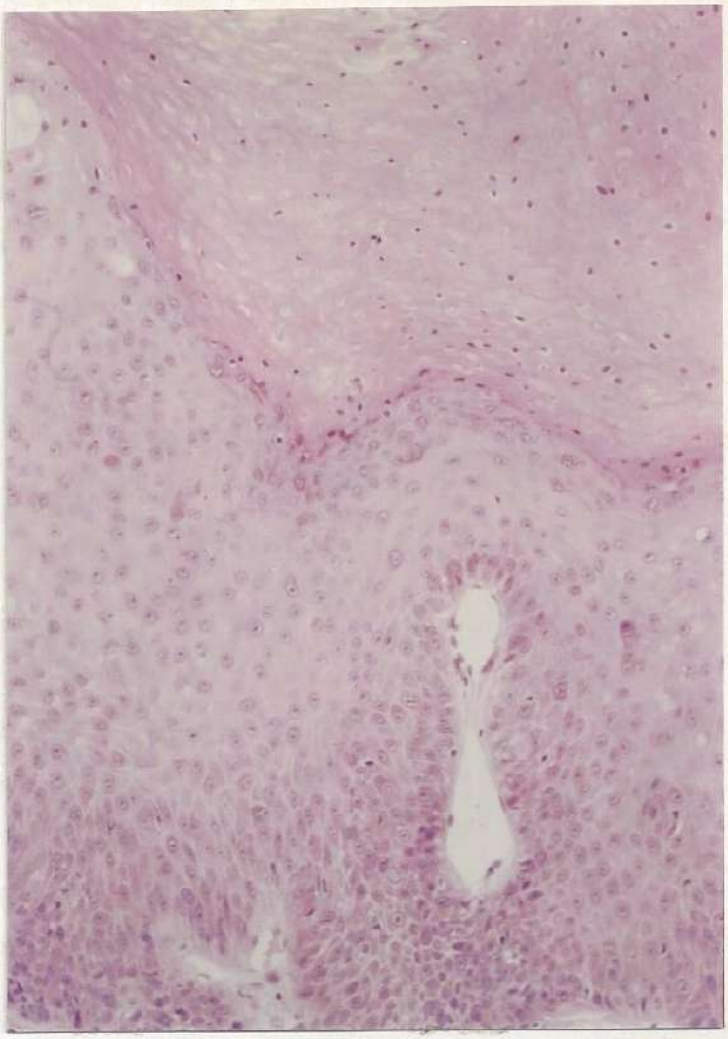


Fig. 1. Hyperkeratosis of the laryngeal mucosa.
(x 100 magnification)

but now that the indications are clearer, it is being practised more frequently (20). A more recent development is the Staffieri techniques (47) of surgical rehabilitation of speech after total laryngectomy. His procedure has success rates of 60-90% so far and has a promisingly wide oncological spectrum of indications.

X-rays were discovered by Röntgen in 1895, Their use in treating cancer was not immediately realised. Newton and Company developed tubes to treat cancer of the larynx between 1910 and 1911. Following this development, sporadic use of X-ray therapy in cancer of the larynx was practised but with devastating untoward reactions.Coutard in 1919, administered post-operative radiotherapy to a patient with advanced laryngeal carcinoma. He was so impressed by the result that by 1922 he had already treated 32 patients. In one series of 6 patients with advanced glottic carcinoma, three were alive for 14 years-a very good result indeed. On the basis of Coutard's fractionation technique, radiotherapy for laryngeal carcinoma was developed (16).Between 1930 and 1950, Coutard's original work was carried out in Western Europe and America using different types of equipment. From the experiences of these various workers, different equipments and methods of radiation therapy have been developed. X-rays have penetrating powers depending upon the voltage at wich they are produced. Low voltage therapy units generate rays up to 100 KV which are used exclusively for skin tumours. The high voltage (250 KV) generators produce X-rays that penetrate deeper and although suitable for laryngeal cancer therapy, they tend to produce mucosal reactions and a considerable amount of energy is absorbed by bone.

The supervoltage therapy was developed in the hope of avoiding these effects and machines such as the linear accelerator and betatron produce electron speeds which correspond to voltages of the order of 8.000.000 volts. Finzi and Harmer (21), in 1928, demonstrated that radium applied by their fenestration operation could cure early cancer of the larynx without disaster. This method is no longer used in the treatment of laryngeal cancer. Megavoltage therapy was developed to meet the requirements of gamma radiation produced by teletherapy units and X-rays from the bigger supervoltage machines. The production of cobalt 60 from the uranium pile provided a source of gamma-rays comparable with that produced by the more expensive and bulky X-ray machines. The maximum dosage from a cobalt unit is developed 4 mm below the skin surface. This makes it ideal for treating deep seated tumours including laryngeal carcinomas.

Further developments in radiotherapy have included use of drugs like synkavit, insulin, steroids, flagyl and 5-fluoro-uracil to sensitize malignant cells to ionizing radiation. Hyperbaric oxygen has been shown to sensitize the radioresistant anoxic tumour cells (22). These new techniques await the test of time before they can be critically evaluated.

1.10.CLINICAL NOTES.

1.11.INCIDENCE.

Cancer of the larynx accounts for about 2% of all reported malignant disease (21). Evidence from most cancer registries indicate that the incidence of this disease is invreasing particularly among males although the rate of increase varies from one country to another. An increase of 1.8 to 2.3 per 100.000 between 1946 and 1969 in Suskatcherwan, Canada was not significant. In Norway the rate of increase among males was 8% per year between 1965 and 1967. During the same period, the rate of increase of incidence of cancer of the larynx was 5 times hihger in Finland compared to Norway and Sweden (23). In the United States the frequency rate of laryngeal cancer may be increasing to as much as 4% altough this is not apparent in the United Kingdom. There is no obvious reason why the Asian races, particularly the Indians, are more susceptible than other races. The incidence of laryngeal carcinoma in the Indians is as high as double that in the Caucasian races.

1.12.AGE AND SEX DISTRIBUTION.

Laryngeal cancer is a disease of all ages. In a review of the literature, Vermeulen (24) found six cases of laryngeal cancer in the under 20 age group. These cases documented from 1873 to 1966 included 4 males and 2 females. Their age ranged from 9½ to 16 year. Significant was the fact that three of these patients had malignant degeneration of juvenile papillomatosis. Nsamba et al (25), in 1979, added a 12 year old boy with

laryngeal cancer presenting with throat pain and cervical lymphadenopathy.

By and large, most laryngeal cancer cases present in their sixth and seventh decade of live. Males are commoner affected than females, Various authors give the male to female ratio ranging from 8.1 to 17.1 (26, 27, 28). Wynder E.L. et al (29) noted a male to female ratio of 14.9 : 1 between 1956 and 1974. In examining the environmental factors associated with laryngeal cancer in 1976, he observed that this ratio had declined to 4.6 : 1 and ascribes this to the fact that more women are cigarette smokers in the cancer age group than 20 years ago. The peak incidence for laryngeal cancer in females is a decade younger than in the males.

1,13.AETIOLOGY.

It is not at present know what causes cancer and laryngeal cancer is not exempted from this fact. The multiple factors associated with laryngeal cancer are environmental and relate to one form of mucosal irritation or another. Heavy tobacco smoking, alcohol consumption, ingestion of spices, exposure to asbestos, vocal cord straining and exposure to dust are the most investigated factors.

Tobacco smoking has been found to lower the cellular immune responses and induction of tumours in laboratory animals and man (30) when exposed for a long time. The mechanism by which tobacco smoke exerts this effect on the immunocompetent cells is not clear but it is thought that the cellular immunity is initially stimulated and on prolonged exposure

exhaustion of the finite immune quantum results. Subjects smoking more than 20 cigarettes per day have a greater risk of developing laryngeal cancer than those smoking less, (29, 31, 32, 33) and cigar smokers stand an even lesser risk when compared to cigarette smokers (33).

Alcohol has been found to be immunosuppressive and it is postulated to be a cofactor in the pathogenesis of cancer (30). Both alcohol and tobacco smoke are irritants to the mucosa and seem to synergetically exert their effect as shown by the fact that alcoholics and smokers have a greater risk of developing cancer of the upper aerodigestive tracts than alcoholics and smokers considered separately (29, 31, 32).

Asbestosis has been associated with pulmonary carcinoma and laryngeal cancer. P.M. Stell et al (34) conducted a controlled retrospective study of 119 patients with laryngeal carcinoma. 27.7% of the cases had significant exposure to asbestos as compared to 2.5% of the control series but points out that this study was based on a small number of male patients. Similar resultst were obtained by Shettigara, P.T. et al (35) who found that 10 patients out of 43 patients with laryngeal carcinoma had been exposed to asbestos and none among the controls. According to these studies the maximum age of onset of the laryngeal carcinoma in patients exposed to asbestos was a decade less than observed in patients without exposure to asbestos. The latent period between exposure and development of laryngeal carcinoma was as long as 30 years in which respect those patients who are heavily exposed to asbestos may die of pulmonary complications (asbestosis) before laryngeal carcinoma starts.

Very prolonged vocal straining with severe chronic laryngitis and previous irradiation of the neck may as well contribute to development of laryngeal cancer.

1.14.PATHOLOGY.

Laryngeal cancer lesions can be exophytic, ulcerative or infiltrative. Most lesions are exophytic. Histopathologically 98% are epitheliomas and 2% include adenocarcinomas, malignant lymphomas, fibrosarcomas, chondrosarcomas, plasmacytomas, malignant melanomas and where Kaposis sarcoma is common, a visceral lesion may be found in the larynx.

Broders, in 1920, proposed a scheme of grading squamous cell carcinomas of the lip based on the percentage of undifferentiated cells. Thus:

Grade	% of cells undifferentiated
1.	0-25%
2.	25-50%
3.	50-75%
4.	75-100%

This scheme has been applied in carcinomas of the larynx but in a modified form to denote only three main categories; "well" "moderately"and"poorly" differentiated squamous cell carcinoma. Where 100% of the cells are undifferentiated the lesion is anaplastic.

About 80% of the glottic lesions are well differentiated squamous cell carcinomas. 55% of the lesions elsewhere in the larynx are well differentiated.

Spindle cell carcinoma (Pseudosarcoma) is a pleomorphic variant of squamous cell carcinoma. These lesions presenting as polypoid or pedunculated lesions (36) are difficult to diagnose and treat. There is a high incidence of local recurrences following radiotherapy in which respect most authors recommend surgery for such lesions.

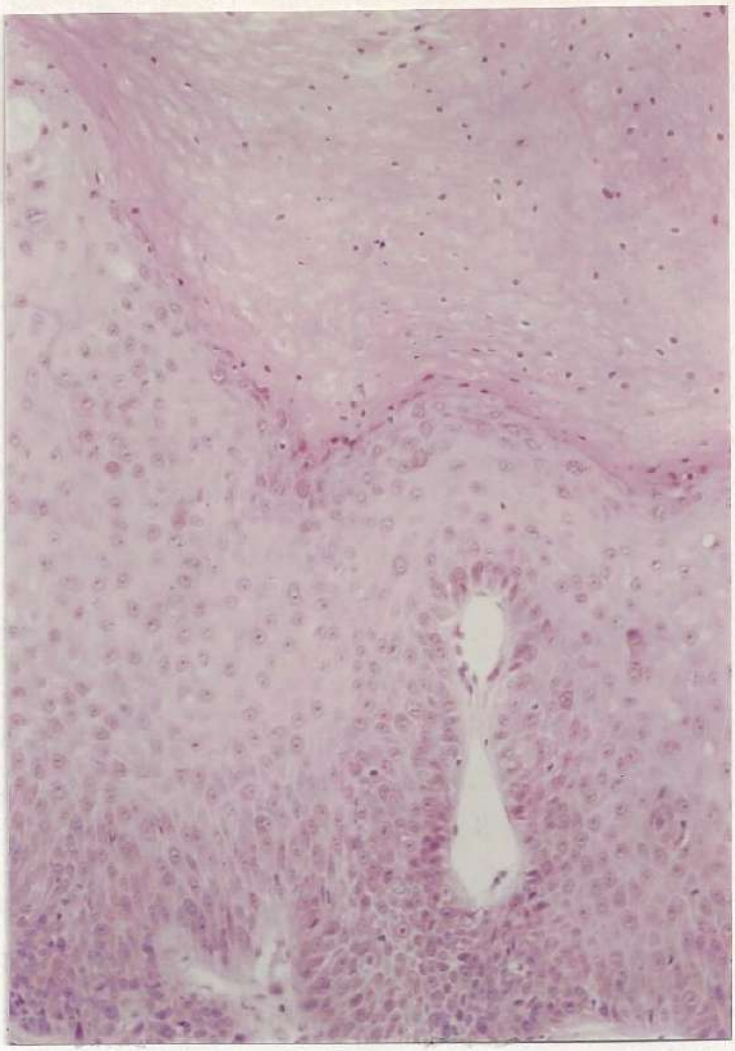


Fig. 1. Hyperkeratosis of the laryngeal mucosa.
(x 100 magnification)

Pseudosarcomas have tendencies to lymph node and pulmonary metastasis. Verrucous Carcinoma of the larynx is another variant of squamous cell carcinoma. Characteristically it is an exophytic warty tumour showing marked hyperkeratosis with thick club-shaped processes of squamous epithelium. that invade the surrounding structures.The epithelial cells are well differentiated with minimal nuclear abnormalities. They have a better prognosis than other types of squamous cell carcinomas. Metastasis is rare with this tumour and is even of late occurrance. Anaplastic transformation occurs with radiotherapy (37, 38) which in certain situations end up fatally. However Mihaly Bak Jr. et al (39) described a case of verucous carcinoma treated by radiotherapy with no apparent untoward effects or recurrence over a period of $2\frac{1}{2}$ year. Most authorities avoid radiotherapy for such lesions.

Adenocarcinomas of the larynx present three histological types: adenocarcinoma, cylindroma and mucoepidermoid carcinoma. Probably adenocarcinomas originate from the minor salivary glands or mucous glands and commonly arise from the supraglottic region. These tumours present late, are ascribed with high local recurrence rates and spread insiduously (40). Cylindromas are very slow growing but spread along the nerve sheaths and through the haematogenous route. This explains why they have very poor prognosis.

Certain laryngeal mucosal changes associated with chronic laryngitis have been associated with malignant conversion. Delamarre, (41), has categorized these epithelial changes into three main groups as follows:

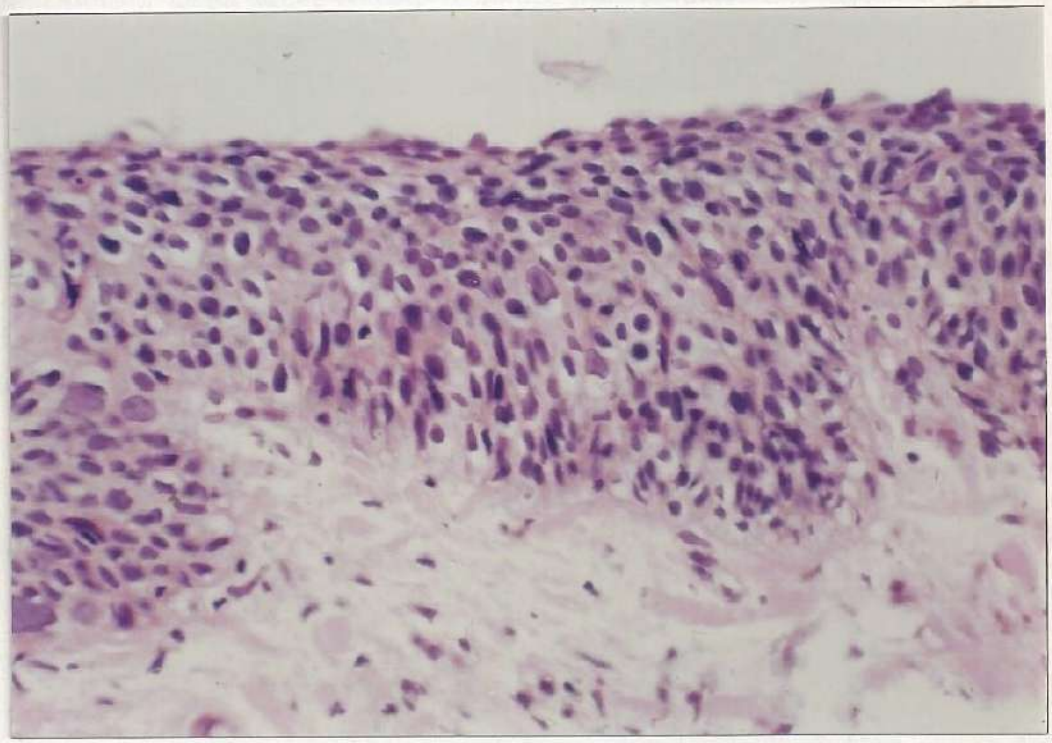


Fig. 2.

Carcinoma in situ. (x 100 magnification).

Note: Atypia, polymorphism, hyperchromasia with loss of polarity.

Grade I. Squamous cell hyperplasia.

Grade II. Squamous cell hyperplasia with occasional cellular atypia.

Grade III. Precancerous epithelium (cytocellular carcinoma).

Thus, with serial vocal cord striping or biopsies in chronic laryngitis patients, histological findings can direct the attending surgeon when therapy must be changed to that of laryngeal carcinoma. In this respect, the terminology must be clearly understood.

a) LEUKOPLAKIA: means white patches. It is used only in clinical practice.

b) HYPERKERATOSIS: means exuberant keratinization of the surface of the vocal cord. Some authorities prefer to use the term keratosis instead of hyperkeratosis because under normal circumstances, keratin never forms on the vocal cord. Keratosis is a change occuring on squamous epithelium in response to chronic irritation.

c) ACANTHOSIS: connotes thickening of the prickle cell layer.

d) DYSKERATOSIS : means premature keratinization in the prickle cell layer.

e) PARAKERATOSIS: means the nuclei of the keratinized cells are still retained.

f) CELLULAR ATYPIA: means faulty maturation, nuclear aberrations, irregularity, hyperchromatism and abnormal mitoses.

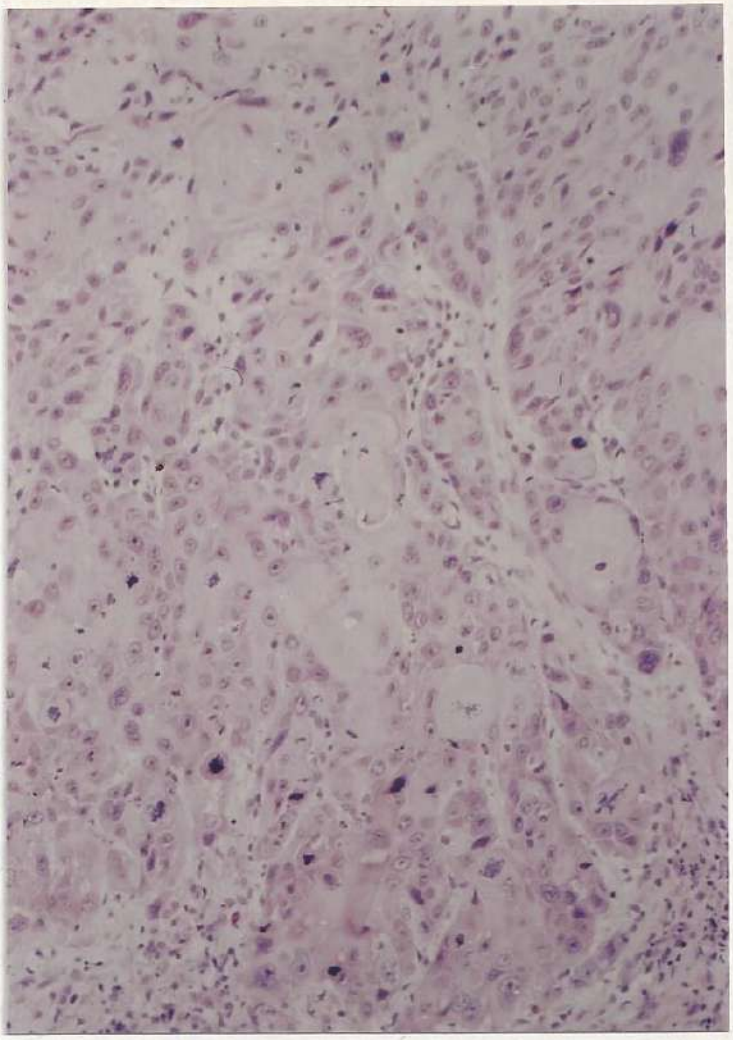
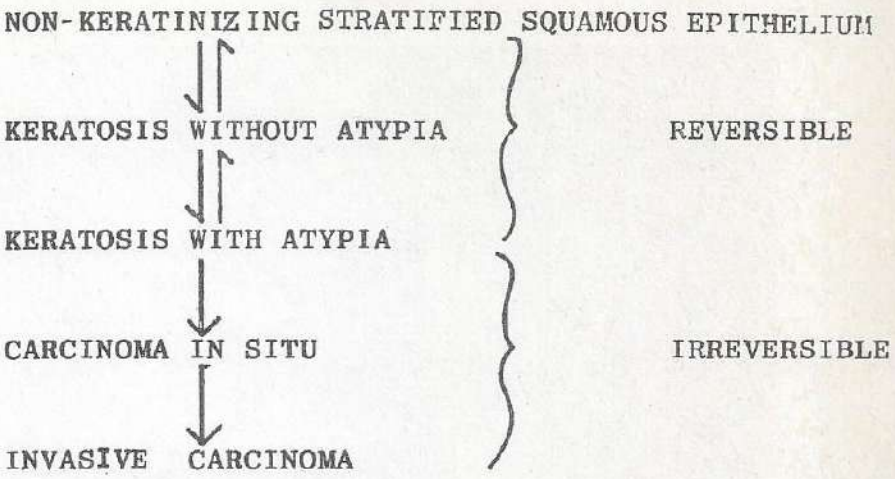


Fig. 3.

Well differentiated squamous cell carcinoma of the larynx.

- Evident invasion.
- Squamous cell differentiation (maturation) with groups of large eosinophilic nuclei as well as attempted horn pearl formation.

R.C. Henry (42) has suggested a possible pathway for these epithelial changes as follows:



It will be noted that in this scheme, keratosis with atypia is potentially a precancerous lesion. 28.4% of such lesions convert to invasive carcinoma. Knowledge regarding the patterns of growth and spread of laryngeal cancers has been gained from whole organ serial sections (43, 44). Within the laryn local extension of laryngeal cancer occurs along the surface or by submucous infiltration. The cartilaginous framework definitely restricts extension. Glottic lesions spread anteroposteriorly with minimal tendency to invade the false vocal cord. However, involvement of the arytenoid and anterior commisure is common. Glottic lesions with mobile cord are found superficial to the conu elasticus which forms a barrier to deeper spread. Thus glottic lesions with a mobile cord are easily resectable via a laryngofissure.

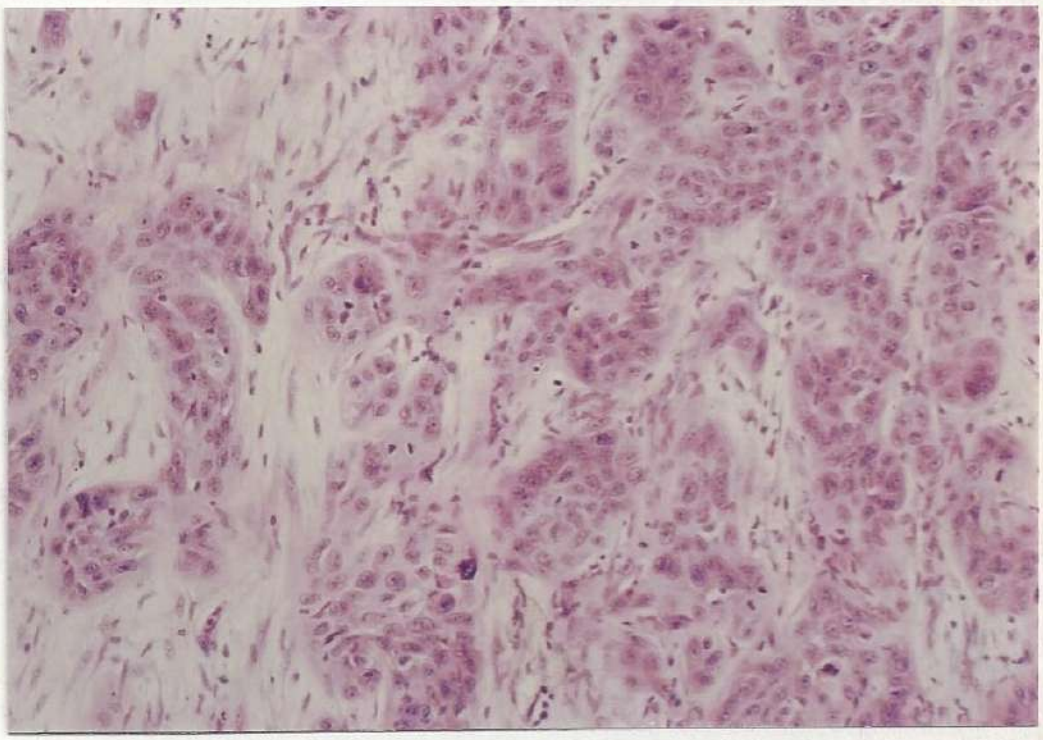


Fig. 4.
Moderately differentiated squamous cell carcinoma of the larynx. - Uniform population of atypical malignant cells with prominent eosinophilic nuclei.

Limitation of the movements of the vocal cord may be due to the weight of the tumour mass or direct infiltration of the thyroarytenoid muscle by cancer. Direct extension of the tumour along the superior surface of the vocal cord does limit movements of the cord.

Fixation of the vocal cord suggests complete replacement of the thyroarytenoid muscle by tumour, direct invasion of the thyroid cartilage, subglottic extension of 1 cm. or more anteriorly or 5-6 cm. posteriorly or radiation fibrosis with residual tumour.

Supraglottic cancer tends to remain confined entirely above the sinus Morgagni and anterior commissure. Where there is limitation of the vocal cord or fixation, the tumour is already transglottic. The pre-epiglottic space is readily involved but only very occassionally will the thyroid cartilage become involved. The clinical significance of this behaviour is that supraglottic tumours with a mobile cord are amenable to supraglottic laryngectomy except for anaplastic carcinomas which tend to spread submucously and tumours located on the petiole.

Subglottic lesions invade and fix the vocal cord. 50% invade the thyroid cartilage or cricoid. Invasion of the conu elasticus almost invariably leads to diminution of the vocal cord movements and fixation.

Metastatic spread from laryngeal cancer through the lymphatics is very important from the point of view of therapy and prognosis. The tendency to this mode of spread is largely governed by the availability of lymphatics draining the region involved. The greater the lymphatic drainage, the greater the tendency to lymphatic spread of a cancer at the respective region. Thus, the true vocal cords are practically devoid of lymph

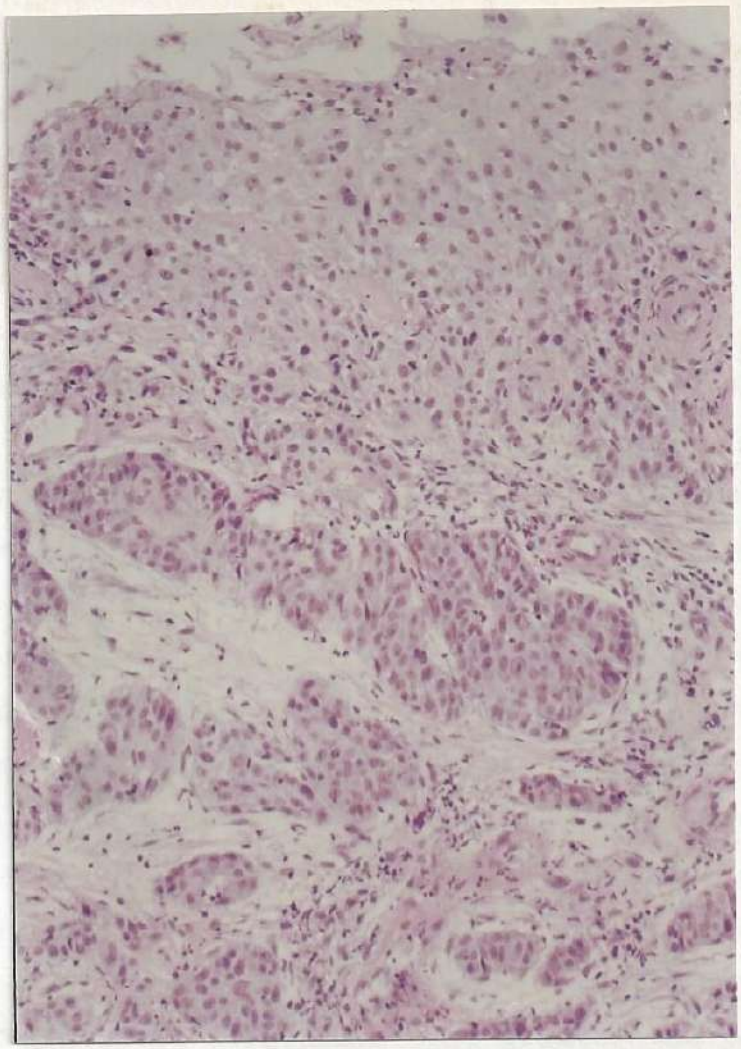


Fig. 5.

Poorly differentiated squamous cell carcinoma of the larynx. Very atypical cells with varying sizes of the cells and their nuclei. Minimal resemblance of the tumour cells to the cells of origin.

vessels. Lesions confined to this region remain localized and thus amenable to local excision via a laryngofissure with good prognosis.
G.B. Snow (45) noted only 5 out of 160 stage III and IV glottic carcinoma lesions with cervical lymph node metastases.
The Supraglottic region has profuse lymphatic drainage via the thyrohyoid membrane to the upper and middle deep cervical lymph nodes. 40% of the stage III and IV supraglottic carcinoma lesions have lymph node metastases (45). Owing to this high frequency of lymph node metastases in cancers of the supraglottic region, some authorities advice prophylactic neck dissection when treating advanced supraglottic carcinoma lesions.
Lymphatic drainage from the subglottis is via the cricothyroid membrane to the pretracheal and paratracheal lymphnodes then to the mediastinal nodes. Lesions of the subglottis are late in presentation and carry very poor prognosis. Only 1% present with cervical lymph node metastases.
Other factors which govern lymphatic spread of laryngeal carcinoma include the size of the primary lesion and the degree of differentiation. Undifferentiated carcinomas show greater tendency to lymph node metastasis than well differentiated carcinomas. The greater the primary lesion, the greater the tendency to lymph node metastasis.
Only 60-70% of the palpable nodes contain carcinoma. Clinically impalpable or occult nodes contain cancer in about 25% suggesting that we can detect only 75% of the lymph node metastases palpably.
Haematogenous spread in laryngeal cancer occurs late with uncontrollable neck disease and only in about 16% of the cases. Lung, liver and bone metastases may be noted up to four years following laryngectomy without evidence of local recurrence.

1.15.CLINICAL PRESENTATION.

-Hoarseness is the main symptom of laryngeal cancer. In glottic lesions it occurs early while in supraglottic lesions, it is a late symptom. It may be slight or absent in lesions involving the marginal zone of the laryngopharynx.

-Throat pain sometimes referred to the ear(s) occurs in supraglottic lesions. It may be associated with increased expectoration and husky voice.

-Dyspnoea is a late symptom particularly with subglottic lesions. It is due to obstruction of the airway by the tumour mass or infiltration and fixation of the vocal cords.

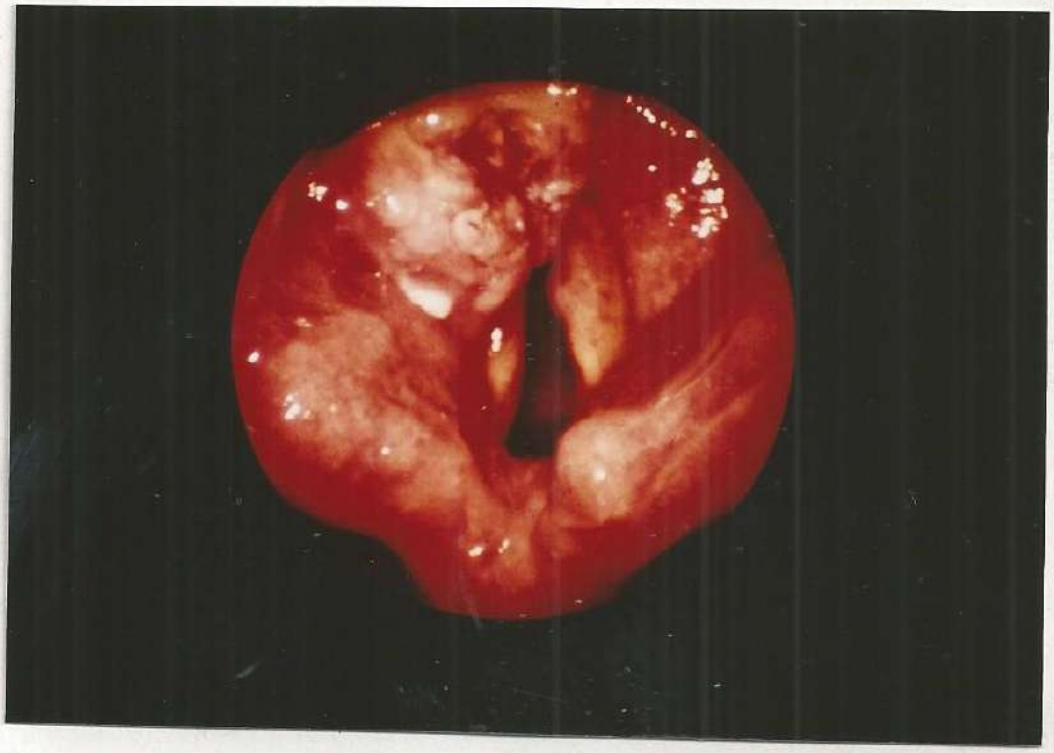
-Dysphagia, loss of appetite, cachexia, foetor of the breath and sometimes haemorrhage occur in advanced disease.

-Cervical lymphadenopathy with minimal throat complaints has been reported in a child (25) but this is rare.

-Some patients are asymptomatic and are found in the course of routine oto-rhino-laryngological examination.

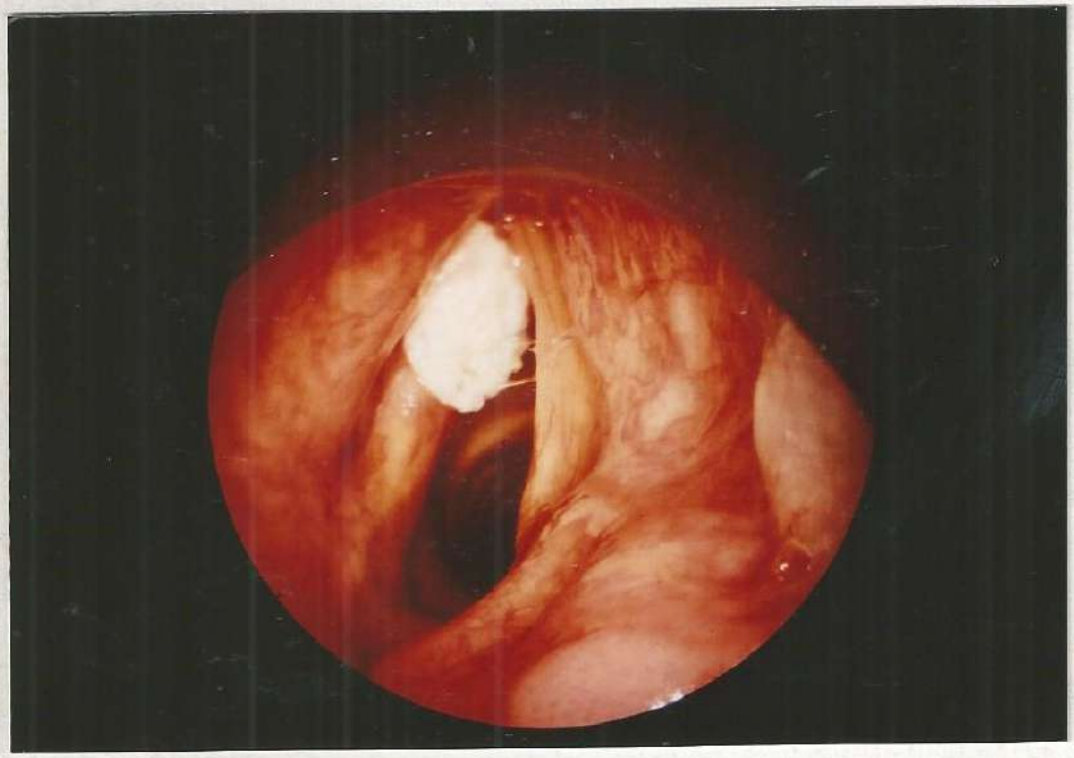
1.16.DIAGNOSIS.

A well taken history is essential. This should include the age and sex of the patient, exposure to possible predisposing factors such as tobacco



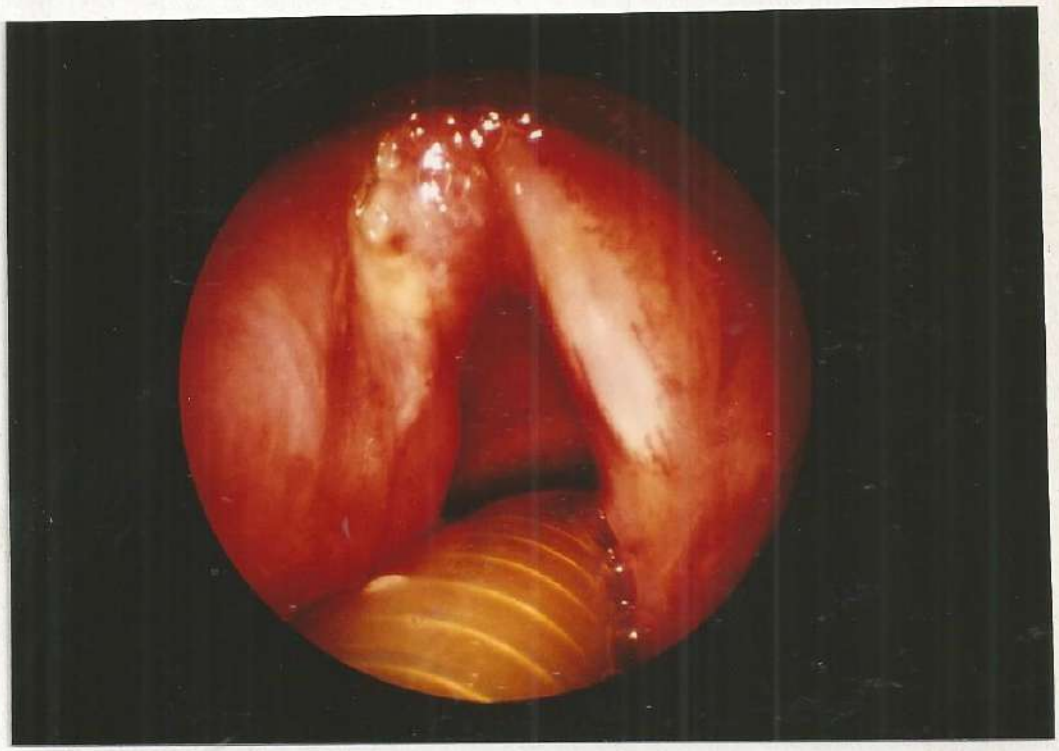
E. 428

Fig. 6. Exophytic supraglottic carcinoma.



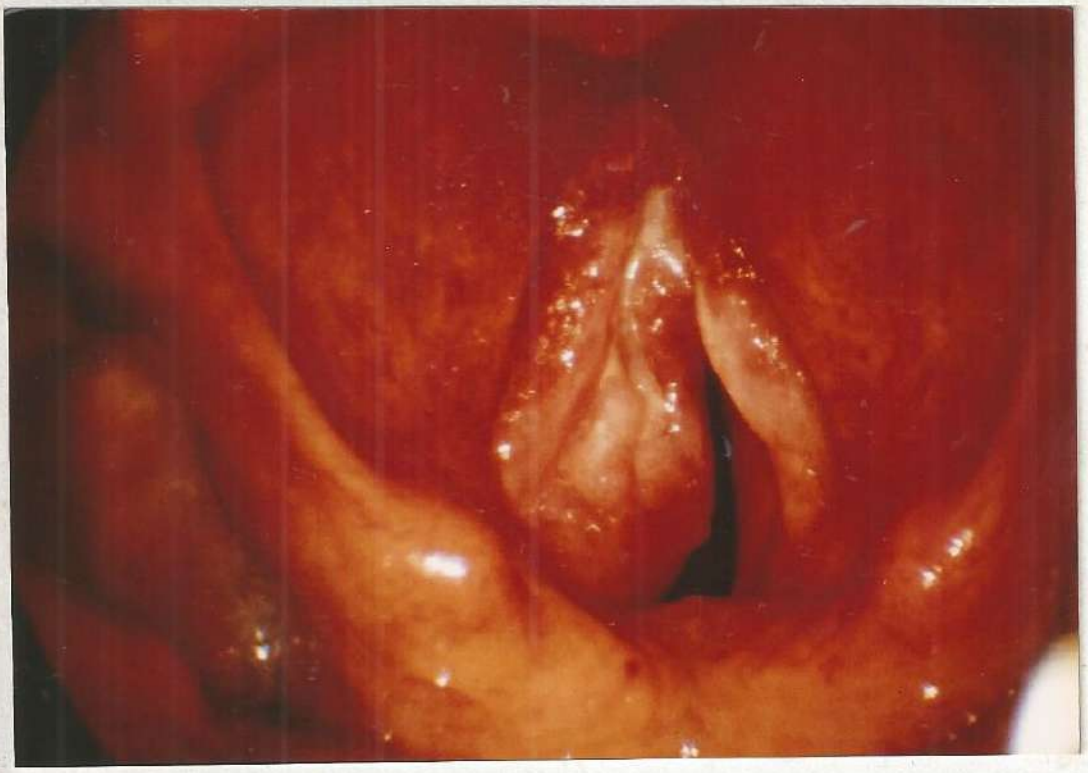
E. 47

Fig. 7. Exophytic glottic carcinoma.



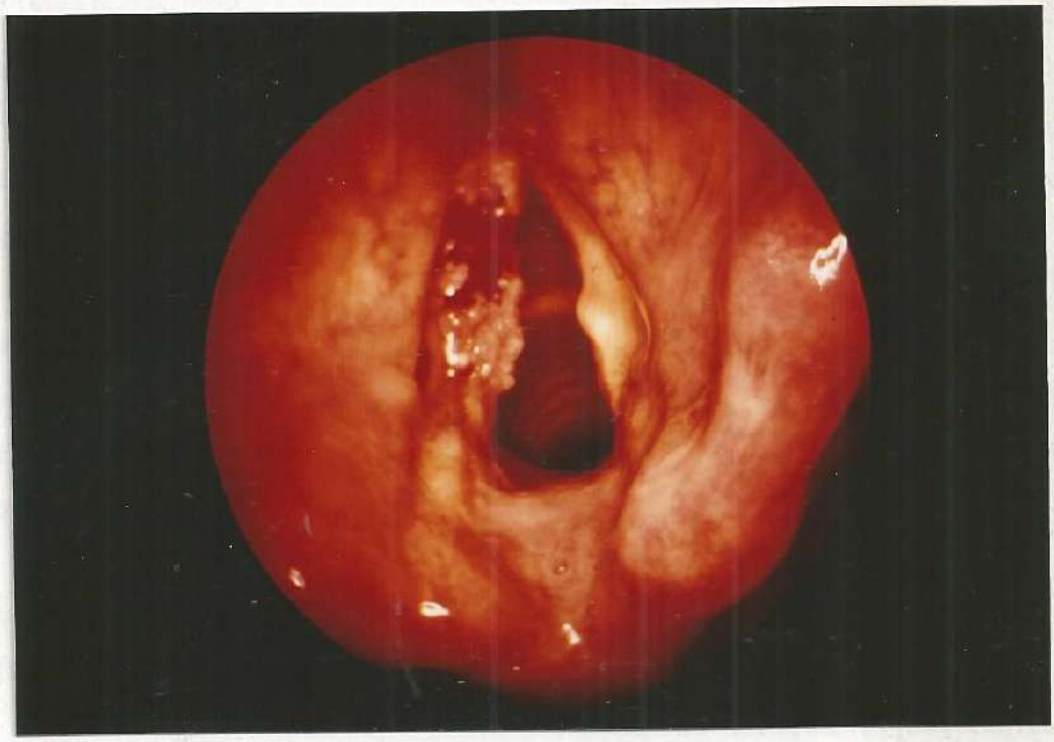
E. 422

Fig. 8. Early carcinoma of the anterior third of the true vocal cord.



E. 452

Fig. 9.Exophytic subglottic carcinoma.



E. 426.

Fig. 10. Ulcerative glottic carcinoma lesion.

smoking, alcohol ingestion, vocal cord straining and exposure to asbestos. Symptoms relating to laryngeal disease (1.15 above) are carefully noted.

Physical examination should include a general E.N.T. examination. Systematic palpation of the cervical lymph nodes must be done. The mobility of the larynx and presence or absence of laryngeal crepitus should be noted. "Dew lap" is a feature of advanced infiltrative growth in the laryngopharynx or floor of the mouth.

Indirect laryngoscopy may reveal an exophytic growth, ulcer, polyp, infiltrative growth or a keratotic lesion. It is vital to note the exact location, extent and appearance of the lesion. Mobility of the vocal cord must be noted.

Direct laryngoscopy or microlaryngoscopy permits the lesion to be studied in detail. This is concluded by inspection of the subglottic space using a 90^{o} bronchoscope optic and taking an adequate and representative biopsy of the lesion for histopathological diagnosis. Where indicated by the extent of the lesion, an oesophagoscopy may be done to evaluate the post-cricoid region and upper third of the oesophagus.

A routine general examination for possible systemic metastases as well as other complicating diseases is vital as this will have a definite influence on the plan of the management. An opinion of a physician should be sought where necessary.

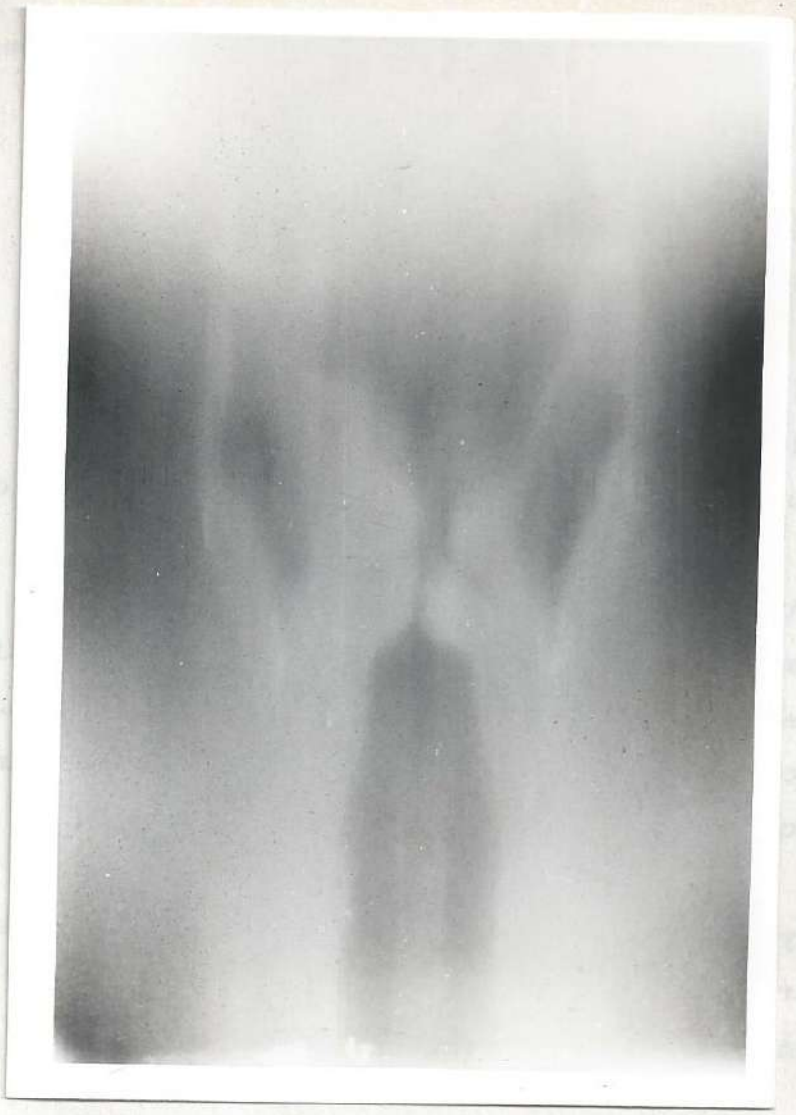


Fig. 11.

1. Tumour of the right true and false cords. Larynx tomogram, phonatory position, with increased bulk of the right hemilarynx with occlusion of the sinus of Morgagni.

The following laboratory investigations are a minimum requirement:

(I) Serological examination for syphilis.

(II) Sputum examination for tuberculosis bacilli.

(III) Full blood count and haemoglobin.

(IV) Blood urea nitrogen and electrolytes.

(V) Urinalysis.

(VI) Serum proteins.

(VII) Electrocardiography.

(VIII) Pulmonary function tests in those patients with chronic bronchitis.

RADIOLOGICAL EXAMINATION.

a) Chest X-ray assists in eliminating or confirming a co-existing pulmonary tuberculosis, a retrosternal mediastinal mass of lymph nodes, metastatic lung or thoracic cage lesions. A concomitant second primary in the lungs may be picked through this noninvasive procedure.

b) Soft tissue X-ray of the larynx apart from showing the patency of the airway may reveal presence of epiglottic tumour, post cricoid tumour or subglottic extension of a glottic tumour.

c) Tomography is of much value in defining the extent of the lesion. The pyriform fossae, valecula, sinus Morgagni and integrity of the laryngeal framework are well depicted. The tumour mass is usually well shown in the tomograms and the mobility of the vocal cords evaluated.

d) Laryngography assists in determining the lower extent of the growth.

Fig. 12.

2. Larynx tomogram.

Small tumour of the right vocal cord;minimal increase in bulk of the right true cord and asymmetry of the Morgagni sinus.

in supraglottic tumours, the integrity of the ventricles, subglottic region and pyriform fossae.

e) Xerography (lateral views) assist in delineating laryngeal lesions. Only the lateral views are useful in evaluating the size of the airway.

1.17.CLASSIFICATION.

The objectives of classifying malignant disease are:

(I) To aid the clinician in planning treatment.
(II) To give some indication of prognosis.
(III) To assist in evaluation of treatment results.
(IV) To facilitate the exchange of information between treatment centres
(V) To contribute to the continuing investigation of human cancer.

The TNM System is based on:

The extent of the primary tumour... T
The condition of the regional lymph nodes...N
The absence or presence of distant metastases... M

The TNM classification Committee of U.I.C.C. revised the classification of laryngeal cancer following a field study of 1645 cases of larynx cancer (This study demonstrated clearly that the best survival was experieced by patients with in situ carcinoma (TIS) 97%. When the tumour was limited to the region of origin, (T1) survival was 94% for glottic cancer and 91% for supraglottic cases. As the tumour spread to other regions of the

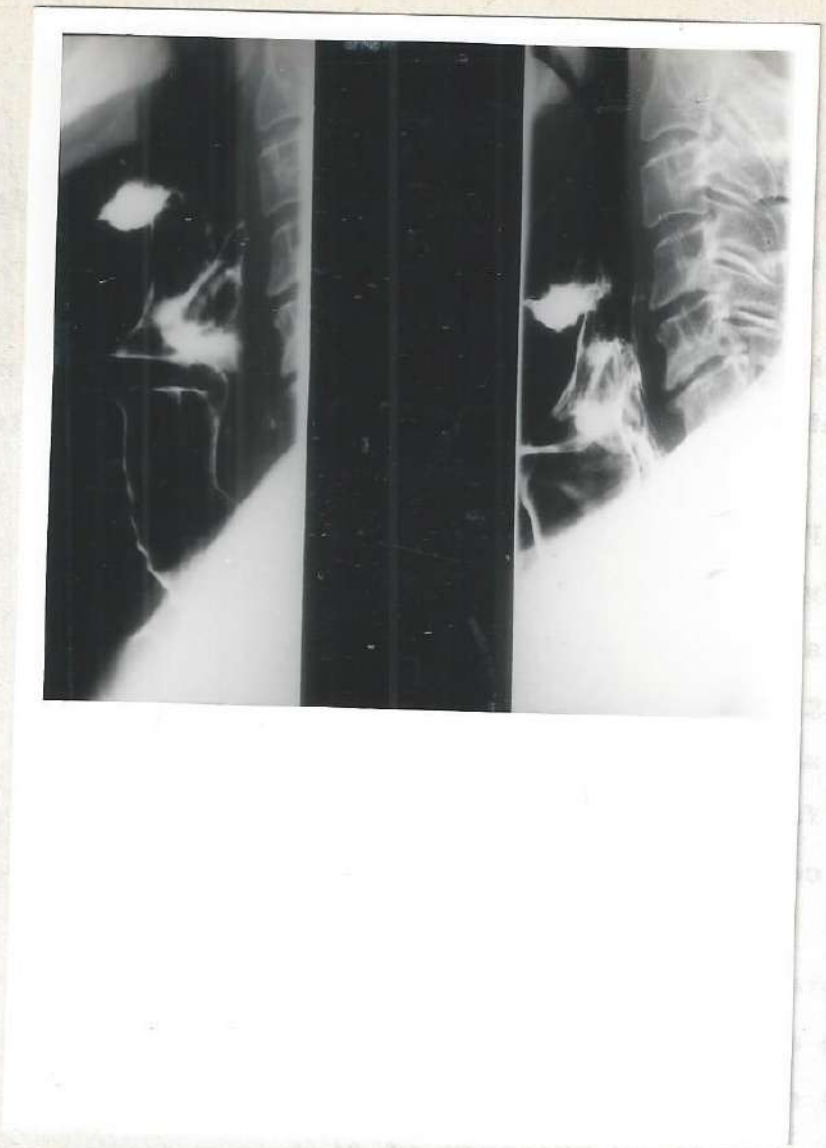


Fig. 13.

3. Same as 2.

Larynx laryngogram - lateral view. Small tumour of the true vocal cord with subglottic extension in the anterior commissure.

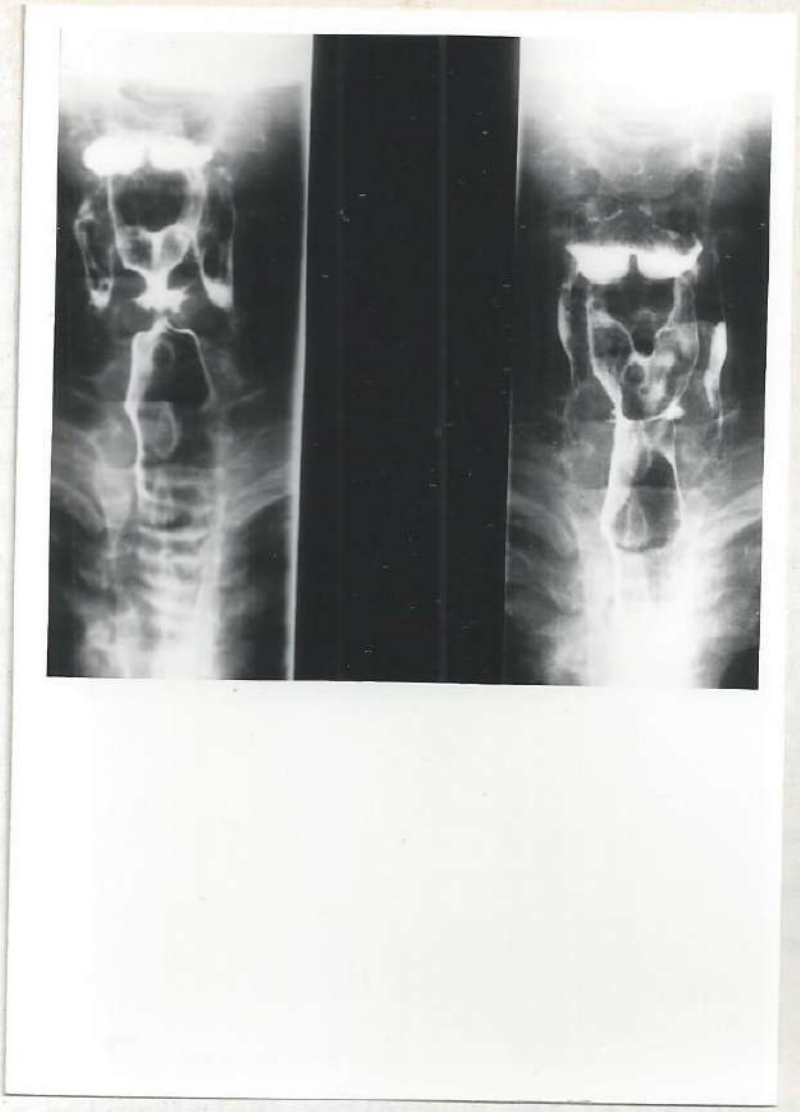


Fig. 14.

4. Laryngogram as 2. PA view

Slight increase in bulk of the right true vocal cord with slight asymmetry of the sinus of Morgagni.

larynx but still confined to the larynx without fixation (T2) survival was 85%-82%, when the larynx was fixed and the tumour still within the larynx (T3) survival was 65%-74% and as the tumour spread outside the larynx (T4) survival dropped to 40%-55%. Presence of homolateral, bilateral or contralateral nonfixed nodal metastases reduced the survival to ± 50%. Fixed regional metastases reduced the survival to 21%. No survivors were observed in cases of bilateral and fixed nodal metastases. When the factors were combined, survival progessively decreased thus stage I-94%, stage II-85%, stage III-59% and stage IV-9% for glottic cancer. For supraglottic carcinoma, the survivals were accordingly 91%, 82%, 49% and 9%. It seems that the behaviour of supraglottic cancer lesions is slightly different from glottic cancer lesions.
For accurate documentation, the limits of the larynx are:
(I) Anteriorly: the posterior surface of the suprahyoid epiglottis, the thyrohyoid membrane, the anterior commissure, the anterior wall of the subglottis and the anterior arch of the cricoid.

(II) Posterolaterally: aryepiglottic fold, arytenoid, interarytenoid space and the posterior surface of the subglottis including the membrane covering the cricoid.

(III) Superolaterally: tip of the lateral border of the epiglottis inferiorly.

(IV) Inferiorly: plane through the inferior edge of the cricoid cartilage.

The regions of the larynx and their respective sites are:

A. SUPRAGLOTTIS (161.1)

(I) Epilarynx

a) Posterior surface of the suprahyoid epiglottis and the tip.

b) Aryepiglottic fold.

c) Arytenoid.

(II) Supraglottis excluding epilarynx

d) Infrahyoid epiglottis.

e) Ventricular bands.

f) Ventricular cavities (Sinuses of Morgagni).

B. GLOTTIS (160.0)

a) Vocal cords.

b) Anterior Commissure.

c) Posterior Commissure.

C. SUBGLOTTIS (161.2)

For the sake of interpretation, regional lymph nodes for the larynx are the cervical lymph nodes.

Using the data obtained (46), the revised TNM classification for carcinoma of the larynx U.I.C.C. 1974 (confirmed in 1979) was made.

1. SUPRAGLOTTIS.

TIS: Pre-invasive carcinoma.

TO : No evidence of primary tumour.

T1 : Tumour limited to the region with normal mobility.

T1 a) Tumour confined to the laryngeal surface of the epiglottis or to an aryepiglottic fold or to a ventricle or to a ventricular band.

T1 b) Tumour involving the epiglottis and extending to the ventricular cavities or bands.

T2 : Tumour confined to the larynx with extension to adjescent site or sites to the glottis without fixation.

T3 : Tumour confined to the larynx with fixation or other evidence of deep infiltration.

T4 : Tumour with direct extension beyond the larynx.

Tx : The minimum requirements to assess the primary tumour can not be met.

2. GLOTTIS.

TIS: Pre-invasive carcinoma (carcinoma in situ).

TO : No evidence of primary tumour.

T1 : Tumour confined to the region with normal mobility.

T1a: Tumour confined to one cord.

T1b: Tumour involving both cords.

T2 : Tumour confined to the larynx with extension to either supraglottis or subglottis with normal or impared mobility.

T3 : Tumour confined to the larynx with fixation of one or both vocal cords.

T4 : Tumour with direct extension beyond the larynx.

Tx : The minimum requirements to assess the primary tumour can not be met.

3. SUBGLOTTIS.

TIS: Pre-invasive carcinoma (carcinoma in situ).

T0 : No evidence of primary tumour.

T1 : Tumour confined to the region.

T1a: Tumour confined to one side of the region.

T1b: Tumour with extension to both sides.

T2 : Tumour confined to the larynx with extension to one or both cords.

T3 : Tumour confined to the larynx with fixation of one or both vocal cords.

T4 : Tumour with destruction of cartilage and/or with direct extension beyond the larynx.

Tx : The minimum requirements to assess the primary tumour can not be met.

N-Regional Nodes.

NO : No evidence of regional lymph node involvement.

N1 : Evidence of involvement of mobile homolateral regional lymph nodes.

N2 : Evidence of involvement of movable contralateral or bilateral regional lymph nodes.

N3 : Evidence of involvement of fixed regional lymph nodes.

Nx : Minimum requirements to assess the regional lymph nodes can not be met.

M-Distant Metastases.

MO : No evidence of distant metastases.

M1 : Evidence of distant metastases.

Mx : Minimum requirements to assess the presence of distant metastases can not be met.

P-TNM: POST SURGICAL HISTOPATHOLOGICAL CLASSIFICATION.

PT : Primary Tumour.

The PT categories correspond to the T categories above.

PN : Regional nodes.

The PN categories correspond to the N categories.

PM : Distant Metastases-as above.

STAGE GROUPING.

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

Unfortunately, the information obtained at operation is not generally considered admissible for clinical classification but may be used as an addition to it. Two aspects of histopathology may be recorded. The symbols refers to the depth of infiltration of the tumour within the organ or tissue while G refers to the pathological grading of the tumour. Thus:

P1 : Tumour confined to the mucosa.

P2 : Tumour involving the mucosa, the submucosa, the muscularis propria and extends into the serosa but does not penetrate through the serosa.

P3 : Tumour penetrates through the serosa with or without invasion of the contiguous structures.

P4 : Tumour involving the whole thickness of the whole hollow viscus without abvious boundaries.

G1 = Low grade malignancy

G2 = Medium malignancy

G3 = High grade malignancy.

While this classification applies to tumours of the stomach (48), it may soon find its usefulness in tumours of the larynx and oesophagus. At present this classification is still at experimental level.

As a rule, all malignancies must be histologically confirmed, identified by the TNM categories prior to definitive therapy and the relevant investigations done. For laryngeal cancer, this includes clinical examination, direct laryngoscopy with or without oesophagoscopy, tomography of the larynx and laryngography. Equally important is a chest X-ray to rule out pulmonary and mediastinal lymph node metastases. Once the TNM category has deligently been applied, it should remain unmodified.

1.18.MANAGEMENT OF LARYNGEAL CANCER.

The management of laryngeal cancer is principally divided into two categories; curative and palliative therapy. Curative therapy is given to those lesions which are amenable to the presently available methods of therapy with subsequent cancer cure. Palliative therapy is given to those lesions whose extent is beyond cancer cure by the presently available methods of cancer treatment.

The method of curative therapy applied depends principally on the available facilities, the site and extent of the lesion and the histological

differentiation of the tumour. Other factors include the physiological age of the patient, the fitness of the patient for the respective modality of therapy, psychological as well as personal factors.
The presently available methods of curative treatment of laryngeal cancer include radiotherapy, surgery and a combination of radiotherapy and surgery.

A) RADIOTHERAPY.

Primary radiotherapy is indicated in early laryngeal cancer, namely TIS, T1NOMO, T2NOMO glottic, supraglottic and subglottic squamous cell carcinoma lesions. Adenocarcinomas in general do not respond to radiotherapy. Verrucous cell carcinoma converts to anaplastic transformation when treated by radiotherapy (37,38) while spindle cell carcinoma (pseudosarcoma) have high tendencies to recur following radiotherapy (36).
The irradiation is administered to the tumour bearing volume using two parallel opposing fields. The field size ranges from 6 cm x 8 cm to 7 cm x 9 cm depending on the extent and the presence of palpable nodes. Usually a total tumour dose of 6000 to 6500 rad is delivered in 6 to 7 weeks.
The results of radiotherapy depend on the site and stage of the lesion (49). The absolute and relative five year survivals for T1N0 glottic carcinoma are 78% to 86% respectively. The corresponding survivals with primary surgery are 83% and 85%. With T2N0 glottic lesions the absolute and relative five year survivals are 63% and 71% with radiotherapy while the corresponding survivals with primary surgery are 59% and 69%.

For supraglottic carcinoma the five year survivals (absolute and relative) for T1NOMO is 65% and 73% respectively. The corresponding survivals for the same lesions with primary surgery are 59% and 71% respectively. For T2NOMO lesions, the survivals are 61% and 67% while the corresponding survivals with surgery are 61% and 75%.

Subglottic lesions have a grave prognosis because of their tendency to infiltrate downwards and give rise to stomal recurrences. Radiotherapy gives a 5 year survival of 36% while surgery gives a corresponding survival of 42%.

There is a slightly higher survival after surgery because of better selection of the patients with lower incidence of intercurrent disease.

Radiotherapy is preferred for early laryngeal cancer in most institutions because:

(I) A high percentage of the patients are cured and retain normal voice (50, 51, 52).

(II) Many professionals including politicians, lawyers, teachers, preachers and telephone operators are able to resume their work succesfully.

(III) Patients remain ambulatory during radiotherapy and some can continue doing their work.

B) SURGERY.

The various surgical procedures available for laryngeal cancer include laryngofissure and cordectomy, vertical hemilaryngectomy, supraglottic laryngectomy and total laryngectomy. Laryngofissure and cordectomy is mainly indicated in early glottic lesions. It is rarely done as a primary form of therapy as such lesions are treated by radiotherapy. Supraglottic laryngectomy is indicated for supraglottic carcinoma without involvement of the true vocal cord or submucous extension as noted in anaplastic carcinomas.

Total laryngectomy is indicated in advanced (T3 and T4), transglottic and subglottic lesions. In most cases surgery is combined with pre-operative radiotherapy.

For T3N0 glottic carcinoma, the absolute and relative survivals are 61% and 69% following primary surgery compared to 50% and 55 % when treated with primary radiotherapy. T4N0 glottic lesions produce survivals of 32% and 35% respectively when surgically treated compared to 8% and 14% corresponding survivals with radiotherapy alone.

T3N0 supraglottic carcinoma produce 5 year survivals (absolute and relative) of 45% and 62% respectively when primary surgery is given. With radiotherapy the corresponding survivals are 36% and 44%.

T4N0 supraglottic lesions produce 5 year survivals (absolute and relative) of 56% and 56% respectively versus 14% and 10% corresponding survivals with radiotherapy.

Definitely in all these advanced but still localized lesions, the outcome following therapy favours surgery. Some authors prefer combined radiotherapy and surgery for such lesions (53, 54) particularly in supraglottic carcinoma.

For T3 and T4 lesions with lymph node metastases (N1) surgery including neck dissection offers a guarded prognosis with 5 year survivals of 42%. With bilateral (N2) and fixed(N3) nodal metastases, the corresponding 5 year survival is 14%. Note the poor prognosis with N3 lesions.

COMBINED RADIOTHERAPY AND SURGERY.

With this regimen, all patients are operated on regardless of the degree of response to radiotherapy. The most preferred procedure is to give the planned patients radiotherapy pre-operatively followed by surgery at various times. Some authors (55, 56, 57, 58) prefer giving a total of 5.500 rads spread over a period of 5 weeks, rest the patient for 6 weeks then operate.

The rationale for radiotherapy is:

1) Pre-operative radiotherapy destroys the most peripheral but oxygenated parts of the tumour wich are most likely to be cut through during surgery and which will cause local recurrences.

2) It reduces the risk of spilling tumour cells during surgery and have risks of tumour implantation reduced.

3) It deals with microscopic metastatic disease within the field of irradation. Radiotherapy is most effective in a nondisrupted field; further reducing the risk of local recurrences.

The objection to pre-operative radiotherapy stems on the various post-operative complications which include pharyngocutaneous fistula, infection and haemorrhage. Frank R. Hendrickson et al (59), basing their study on results of previous work on experimental tumours and clinical material (60) compared the results of two groups of patients treated with 2000 rads and 5000 rads respectively followed 4 to 6 weeks later by surgery. There was no significant difference between these two groups in terms of survival or local recurrences of the tumour. With this regimen, the period of hospitalization is shorter and the devastating post-operative complications are reduced. I. Kazem, P.van den Broek et al (61) have proposed a short intensive treatment schedule in which the patient is given.2.500 rads at daily fractionations of 500 rads over a period of 5 days and surgery two days thereafter . This short intensive radiation therapy is well tolerated, convenient to the patient and devoid of post-operative complications as surgery is carried out before the radiotherapy reactions have occurred.

Combined therapy is indicated in advanced laryngeal cancer lesions (T3, T4,N1,N2) and has been ascribed with superior results when compared to either surgery or radiotherapy given alone in terms of 5 year survivals results (55, 56, 57, 58).

Palliative therapy is given to lesions which are too advanced for curative surgery, radiotherapy or a combination of surgery and radiotherapy. Apart from surgical releaf of airway obstruction by tracheostomy, radiotherapy or chemotherapy may be given. Other methods of palliative therapy include treatment of pain by either anaelgesics (narcotics) or neurectomy of the sensory nerve from the site of the tumour.

2.00 OBJECTIVES

This study was conducted in order to:

I) Evaluate the effectiveness of the therapy for early laryngeal cancer lesions.

II) Delineate any relevant factors influencing the outcome of such a therapy.

III) Determine the rate of second primaries in these early laryngeal cancer lesions.

IV) Decide on a feasible policy for management of such lesions in a new clinical set up at a different environment within the limits of available resources.

2.10 CASE MATERIAL

A total of 218 early laryngeal cancer (T1) cases treated at the Otorhinolaryngological Institute (Head: Prof.Dr.W.F.B. Brinkman) and Radiotherapy and Nuclear Medicine (Head: Prof.Dr.I.Kazem), Nijmegen University Hospital between 1953 and 1978 inclusive were analysed. In this case material are included patients treated during the year 1978 with the participation of the author. The data was retrieved using a specially designed protocol (Appendix I).

2.11 REGIONAL AND ANATOMICAL DISTRIBUTION

Table I shows the distribution of the case material according to the anatomical region within the larynx. 81.7% were glottic lesions while 17.9% and 0.4% were supraglottic and primary subglottic lesions respectively. The noted preponderance of the glottic lesions is consistent with findings elsewhere in Netherlands (27,62). Apparently the proportion of the glottic lesions to supraglottic lesions is much higher in these T1 case material than expected. All stages of larynx cancer as seen at this University Hospital show proportions of 65% glottic and 35% supraglottic lesions. Marked geographical differences in the frequencies of supraglottic versus glottic cancer throughout the world have been demonstrated by Till J.E. et al (62).

About 82% of the laryngeal cancers in Stockholm involve the glottis while in Belgrade, the frequency of the same anatomical region involvement is only 40%. The converse is true of supraglottic cancers. No sound explanation is available as yet to justify this apparent discrepancy but one is inclined to believe that the exogenous aetiological factors relating to laryngeal cancer vary from one geographical region to another. The low frequency of the primary subglottic lesions noted in this case material is in agrement with the literature.

TABLE I

REGIONAL AND ANATOMICAL DISTRIBUTION OF THE LESIONS

GLOTTIC	177	(81.7%)
SUPRAGLOTTIC	38	(17.9%)
SUBGLOTTIC	3	(0.4%)
	218	(100.0%)

Tables 2 and 3 show the anatomical distribution according to the site of the glottis and supraglottis involved respectively. For the glottic lesions, the right vocal cord was involved in 87 cases while the left vocal cord was involved in 72 cases. Only in 13 cases were both vocal cords involved. As expected, there was no posterior commissure involvement observed.

Regarding the supraglottic lesions the right side was involved in 13 cases while the left side was involved in 16 cases.

In 8 cases, the lesions crossed the midline and this occurred mainly with involvement of the epiglottis. Note that more than one site was involved in some cases. Neither of the three subglottic cases had lateralisation of the lesion indicated.

TABLE 2

DISTRIBUTION OF THE GLOTTIC LESIONS ACCORDING TO ANATOMICAL SITE

SITE	FREQUENCY
ANTERIOR COMMISSURE	9
MIDDLE 1/3 OF VOCAL CORD	15
POSTERIOR 1/3 OF VOCAL CORD	11
ANTERIOR 1/3 OF VOCAL CORD	30
ANTERIOR + MIDDLE 1/3	44
MIDDLE + POSTERIOR 1/3	10
WHOLE VOCAL CORD	58
POSTERIOR COMMISSURE	0
	177

TABLE 3

DISTRIBUTION OF SUPRAGLOTTIC LESIONS ACCORDING TO ANATOMICAL SITE

SITE	FREQUENCY
FALSE VOCAL CORD	20
EPIGLOTTIS	17
ARYTENOID	3
ARYEPIGLOTTIC FOLD	1

Note that there was only on patient with epilaryngeal cancer included in the supraglottic group.

2.12 SEX DISTRIBUTION

Table 4 indicates the sex distribution according to anatomical region localisation of the disease. There is an obvious male preponderance for every region although no tangible deduction can be made on the few cases with subglottic lesions. It is a universal fact that laryngeal cancer is more common among males. A survey of laryngeal cancer has shown that the incidence amongst females has geographical variations (62). 15% Of all laryngeal cancers seen at Liverpool affect females while the rate in Amsterdam is 3% during the same period. In this material, the rate is 7.8%. While the reason form male preponderance and geographical differences in incidences among females is not clearly established, it would seem very likely that males are more exposed to the exogenous aetiological factors associated with laryngeal cancer such as tobacco smoking and asbestos inhalation and possible alcohol consumption. The large prevalence amongst males (92.2%) in this material conforms with observations elsewhere in Holland (27, 62, 63).

TABLE 4

SEX DISTRIBUTION AND MALE/FEMALE RATIO ACCORDING TO ANATOMICAL REGION

REGION	MALE	FEMALE	M/F : RATION
GLOTTIC (177)	165	12	13.7:1
SUPRAGLOTTIC (38)	34	4	8.1:1
SUBGLOTTIC (3)	2	1	2:1

Table 5 shows a detailed sex distribution according to anatomical region and age in decades.

TABLE 5

AGE AND SEX DISTRIBUTION ACCORDING TO ANATOMICAL REGION

AGE	TOTAL		GLOTTIC		SUPRAGLOTTIC		SUBGLOTTIC	
	M	F	M	F	M	F	M	F
30-39	0	1	0	1	0	0	0	0
40-49	17	5	15	4	3	1	0	0
50-59	66	5	54	3	12	2	2	0
60-69	71	3	60	1	11	1	0	0
70-79	44	3	36	3	8	0	0	0
80-89	2	0	0	0	0	0	0	1
90-99	1	0	0	0	0	0	0	0
TOTAL	201	17	165	12	34	4	2	1
	(218)		(177)		(38)		(3)	

The average age for the patients was 60.2 years.

TABLE 6

DISTRIBUTION OF THE MAIN PRESENTING SYMPTOMS

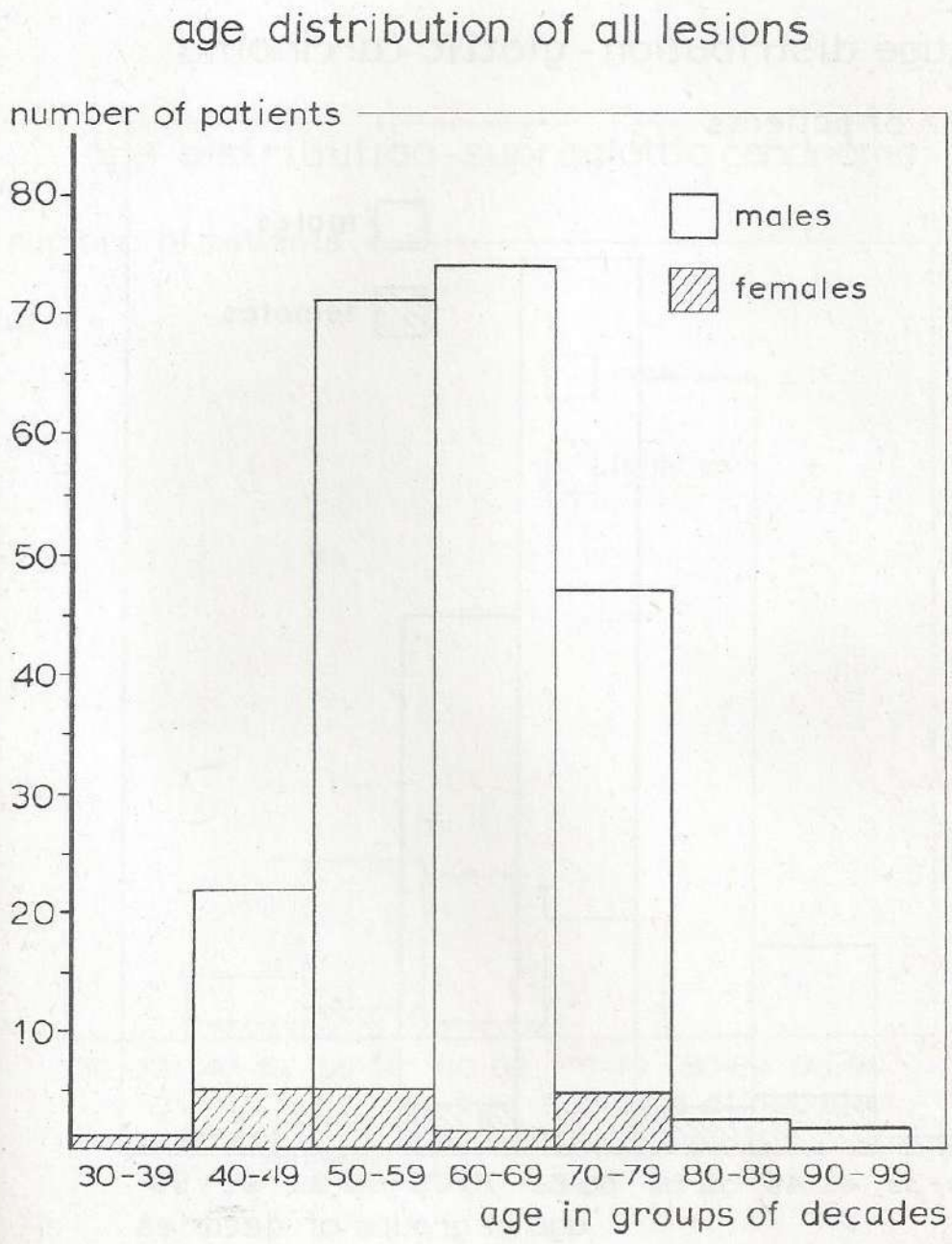
SYMPTOM	GLOTTIC	SUPRAGLOTTIC	SUBGLOTTIC	TOTAL
ASYMPTOMATIC	1	0	0	1
HOARSENESS	176	25	3	204
DYSPNOEA (STRIDOR)	3	0	1	4
DYSPHAGIA	1	11	1	13
PAIN (LOCALISED)	9	11	0	20
(OTALGIA)	1	3	0	4
WEIGHT LOSS	0	1	0	1
COUGH	0	1	0	1
CERVICAL SWELLING	0	1	0	1

2.13 AGE DISTRIBUTION

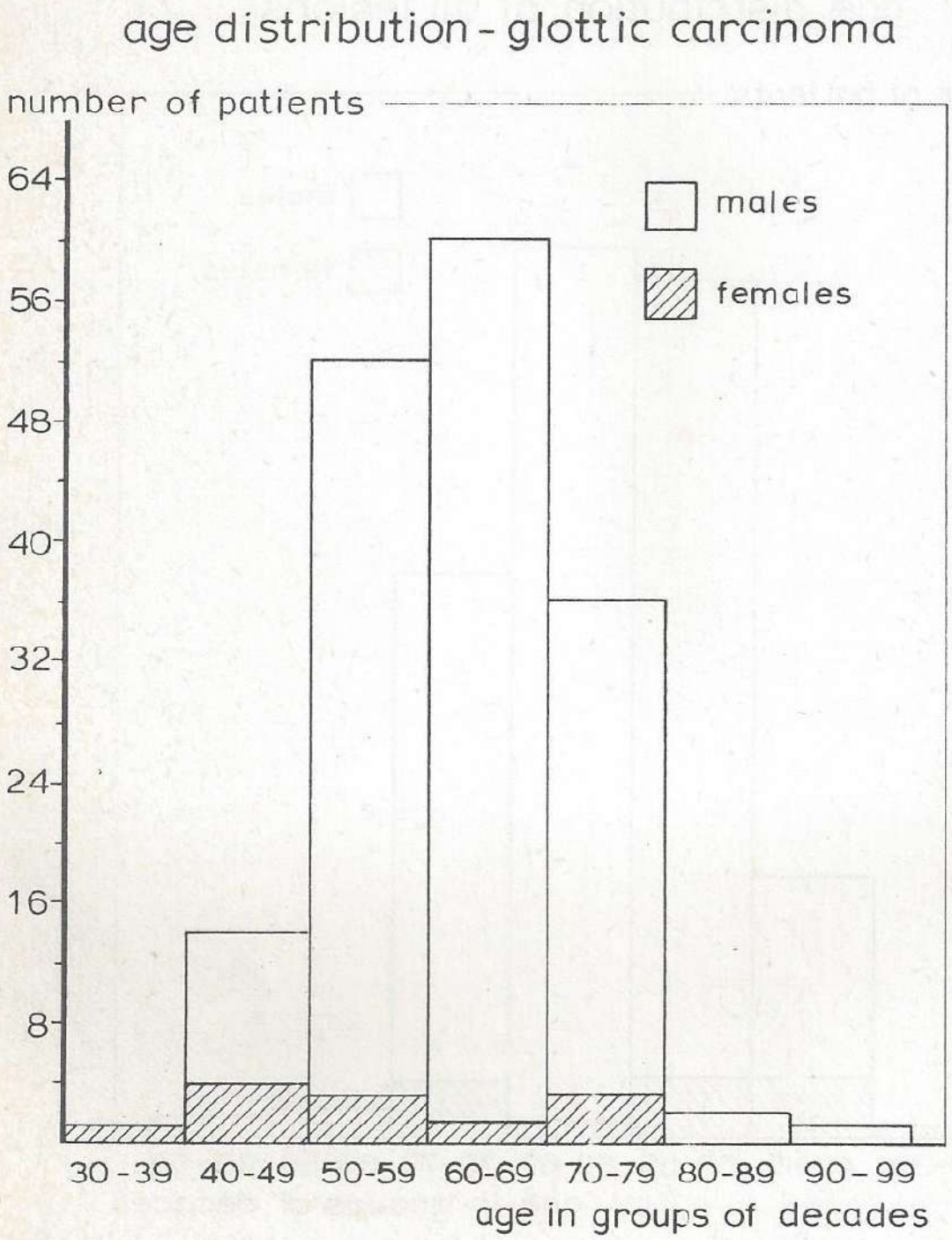
In this case material, the effective age of each patient was that documented when the respective patient was first seen at the Otorhinolaryngological Institute. For the whole case material, the age ranged from 31-94 years with a peak age incidence between the 6th and 7th decade. The available literature (24,25) indicates that only seven patients under the age of 20 have been noted with laryngeal cancer. There was none in this age group noted in our cases. As indicated in histogram I, the youngest patient was a female (Barkeeper!!). Whereas the peak age incidence for laryngeal cancer in females is a decade younger than in the males, this is not evident in this case material probably because there were very few females with almost uniform distribution in all the age groups.

Histograms II and III show the age distribution of the glottic and supraglottic lesions. The peak age incidence for the glottic lesions is within the 6th and 7th decade and is consistent. Whereas supraglottic cancers occur at a younger age than glottic cancers, this is not the case in this material. The peak age incidence for the supraglottic lesions coincides with that for the glottic lesions. Again, there were comparatively fewer patients with supraglottic laryngeal cancer.

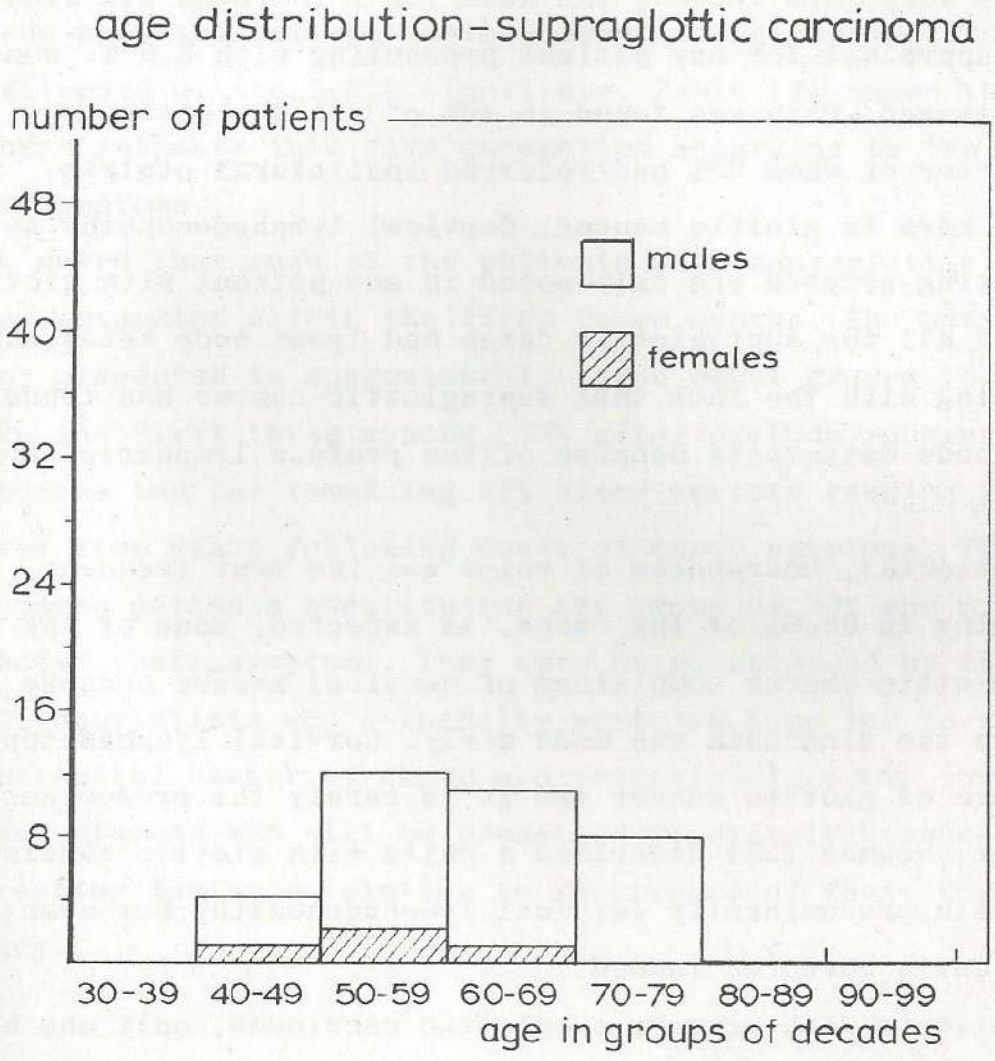
As for the primary subglottic lesions, two were in the 6th decade age group while one was in the 9th decade age group.


age distribution of all lesions
number of patients
80
70
60
50
40
30
20
10
males
females
30-39
40-49
50-59
60-69
70-79
80-89
90-99
age in groups of decades

HISTOGRAM 1


age distribution - glottic carcinoma
number of patients
64
56
48
40
32
24
16
8
males
females
30-39
40-49
50-59
60-69
70-79
80-89
90-99
age in groups of decades

HISTOGRAM 2


age distribution-supraglottic carcinoma
number of patients
48
40
32
24
16
8
males
females
30-39
40-49
50-59
60-69
70-79
80-89
90-99
age in groups of decades

HISTOGRAM 3

2.14.PRESENTING SYMPTOMS.

Table (6) shows the frequency of each of the presenting symptoms. One patient with a glottic cancer was asymptomatic. He was discovered while being clinically appraised for chronic suppurative otitis media. Although this is very rare indeed, the need for a thorough otorhinolaryngological appraisal for any patient presenting with E.N.T. complaints is emphasized. Pain was found in 40% of all the patients with supraglottic cancer of whom 33% had referred ipsilateral otalgia. This symptom is rare in glottic cancer. Cervical lymphadenopathy as the only presenting symptom was only noted in one patient with glottic cancer. 14.2% of all the supraglottic cases had lymph node metastasis. This is in keeping with the fact that supraglottic cancer has tendency to early lymph node metastasis because of the profuse lymphatics draining this region.

For the whole material, hoarseness of voice was the most frequent symphtom occurring in 93.6% of the cases. As expected, none of the patients with glottic cancer complained of cervical masses because in all the cases the diagnosis was made aerly. Cervical lymphadenopathy is a late feature of glottic cancer and it is rarely the predominant symptom. However, Nsamba (25) described a child with glottic carcinoma who presented with predominantly cervical lymphadenopathy but even then the lesion was quite advanced indeed.

Of the three patients with primary subglottic carcinoma, only one had complaints relating to disordered swallowing mechanism.

2.15 DURATION BETWEEN ONSET OF SYMPTOMS AND PRESENTATION TO THE O.R.L. INSTITUTE - NIJMEGEN

All the patients were either referred from their house doctors or ENT specialists elsewhere. The duration of symptoms noted is that between when the patient started complaining to the first time he/she was attended at the O.R.L.-Institute. Table (7) shows the distribution of these patients into five categories according to the duration of their symptoms.

It is noted that most of the patients with supraglottic and subglottic cancer presented within the first three months. The patients with glottic cancer presented in approximately three equal groups. 33% Were attended within the first three months, 33% after periods ranging from three to six months and the remaining 33% after periods ranging from six months to over five years following onset of their symptoms. This does not mean that those patients constituting the group of 33% who presented late neglected their symptoms. They were being attended by their respective E.N.T. specialists who eventually referred them for further management. A substantial number of those who presented late had chronic laryngeal mucosal disease and will be presented separately because they show interesting features relating to recurrence of their disease following therapy.

TABLE 7

DURATION BETWEEN ONSET OF SYMPTOMS AND PRESENTATION

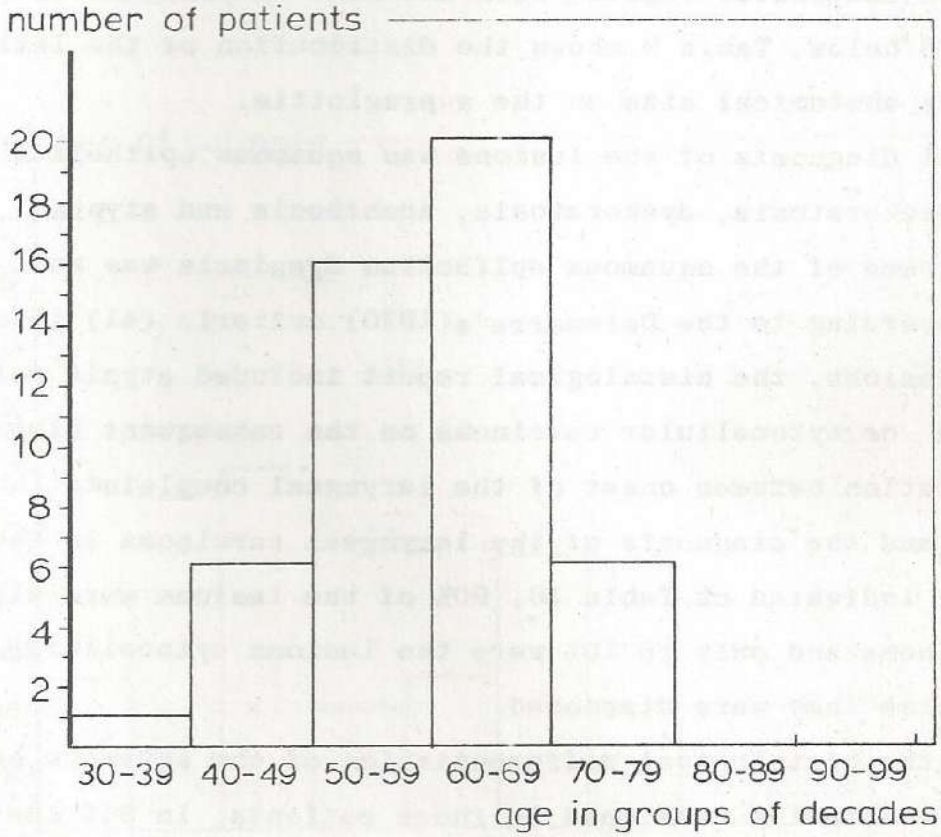
DURATION		GLOTTIC	SUPRAGLOTTIC	SUBGLOTTIC
0 - 3 MONTHS	(92)	66	23	3
4 - 6 MONTHS	(63)	54	9	0
7 -12 MONTHS	(23)	20	3	0
1 - 5 YEARS	(32)	30	2	0
5 YEARS	(8)	7	1	0
	(218)	177	38	3

2.16 CHRONIC LARYNGEAL DISEASE

50 Out of the 218 patients in this case material had chronic laryngeal disease prior to the development of the laryngeal carcinoma. This gives an incidence of pre-existing chronic laryngeal disease of about 23%. 45 Were males while 35 were females. One man had laryngeal tuberculosis that had been curatively treated twenty years prior to the development of the laryngeal cancer. The remainder of the patients had chronic nonspecific laryngeal disease for varying periods of time prior to presenting with laryngeal cancer.

The age distribution of these patients is shown on histogram 4. The youngest patient was a female aged 31 years while the oldest was a man aged 77 years. The peak age incidence is similar to that of the laryngeal cancer in this case material. Mean age incidence is 58.7 years. In 45 patients, the disease was confined to the glottis while in only 5 patients, the disease was on the supraglottis.

age distribution of the patients with chronic laryngeal disease



HISTOGRAM 4

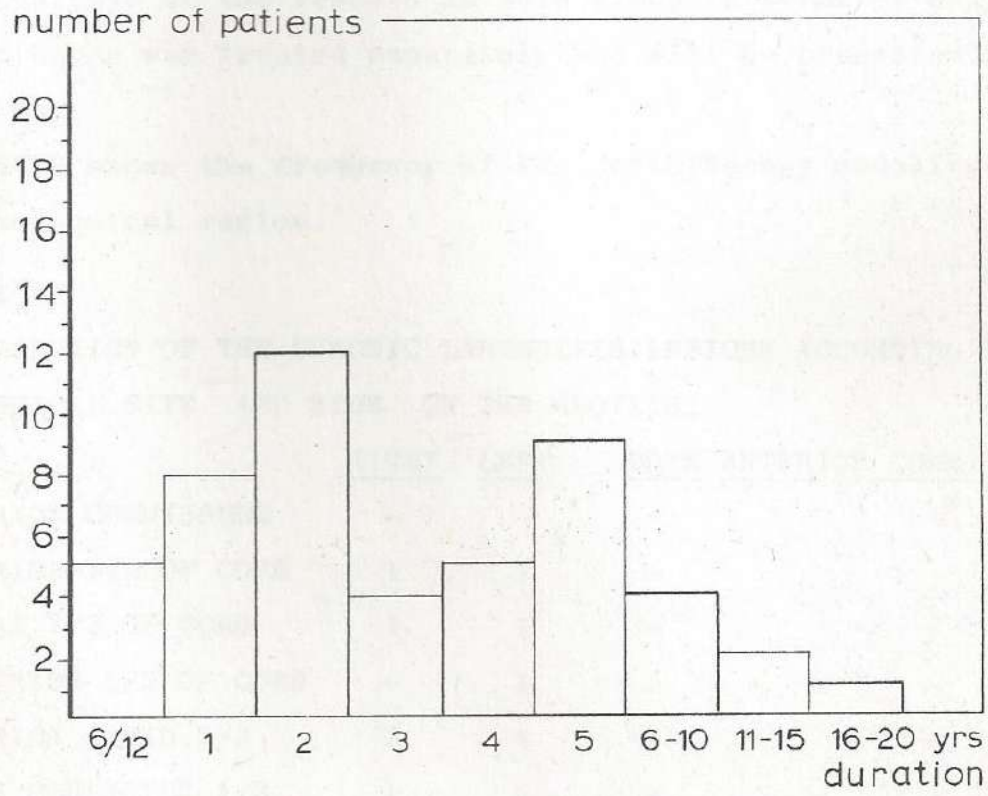
These patients had been on close follow up with microlaryngoscopic examinations and mucosal stripping, each time the material removed examined histologically. For the glottic lesions, 45 males were affected compared to only 5 females. All except 2 females had been smoking 15-20 cigarrettes per day and most of them indulged in moderate to heavy spirituous alcohol drinking. The distribution of the lesions according to the anatomical region, site and side on the glottis is shown on table 8 below. Table 9 shows the distribution of the lesions according to the anatomical site on the supraglottis.

The histological diagnosis of the lesions was squamous epithelium hyperplasia, parakeratosis, dyskeratosis, acanthosis and atypia.

The varying degrees of the squamous epithelium dysplasia was most often graded according to the Delemarre's(1970) criteria (41) into Grades I-III. In all lesions, the histological report included atypia followed by the invasive or cytocellular carcinoma on the subsequent biopsy report. The duration between onset of the laryngeal complaints (hoarseness of voice) and the diagnosis of the laryngeal carcinoma is shown on Histogram 5. As indicated on Table 10, 90% of the lesions were already invasive carcinoma and only in 10% were the lesions cytocellular carcinoma by the time they were diagnosed.

Table 11 shows the histological differentiation of the squamous cell carcinoma that eventually developed in these patients. In 86% the lesions were well differentiated squamous cell carcinoma, 2% moderately differentiated and 12% poorly differentiated squamous cell carcinoma.

duration between diagnosis of chronic laryngeal disease and development of laryngeal carcinoma



HISTOGRAM 5

Two patients (one with glottic carcinoma and one with supraglottic carcinoma) were primarily treated by total laryngectomy and supraglottic laryngectomy respectively. The patient with glottic cancer was treated by total laryngectomy because the tumour was a T1b involving the whole lengths of both vocal cords and he had had radiotherapy for submandibular lymphadenopathy more than 20 years previously. Whether the cancer in this patient was radiotherpay induced or not remains a matter of speculation. The remainder, 44 glottic lesions and 4 supraglottic lesions, were treated by primary radiotherapy (KV 250 and Cobalt 60).

The analysis of the results in this group in terms of survivals and recurrences was treated separately and will be presented in a subsequent section.

Table 12 shows the frequency of the radiotherapy modality according to the anatomical region.

TABLE 8

DISTRIBUTION OF THE CHRONIC LARYNGITIS LESIONS ACCORDING TO THE ANATOMICAL SITE AND SIDE ON THE GLOTTIS.

	RIGHT	LEFT	BOTH	ANTERIOR COMMISSURE	TOTAL
ANTERIOR COMMISSURE	-	-	-	4*	4
ANTERIOR 1/3 OF CORD	1	1	-	-	2
MIDDLE 1/3 OF CORD	1	1	-	-	2
POSTERIOR 1/3 OF CORD	-	1	-	-	1
ANTERIOR + MID.1/3	3	6	4	-	13
MID.+ POSTERIOR 1/3	1	2	-	-	3
WHOLE VOCAL CORD	12	5	4	-	21

* one patient who had a lesion involving the anterior commissure and anterior 1/3 of the right vocal cord is included.

TABLE 9

DISTRIBUTION OF THE CHRONIC LARYNGITIS LESIONS ON THE SUPRAGLOTTIS ACCORDING TO ANATOMICAL SITE.

APIGLOTTIS	1
FALSE VOCAL CORD	3
SINUS MORGAGNI	1

TABLE 10

CLASSIFICATION OF THE SUBSEQUENT CARCINOMA LESION (UICC 1979) ACCORDING TO ANATOMICAL REGION.

	GLOTTIC	SUPRAGLOTTIC	TOTAL
T1aNoMo	33	5	38
T1bNoMo	7	-	7
TIS	5	-	5
	45	5	50

TABLE 11

HISTOLOGICAL DIFFERENTIATION OF THE SUBSEQUENT CARCINOMA ACCORDING TO ANATOMICAL REGION

	GLOTTIC	SUPRAGLOTTIC	TOTAL
1. SQUAMOUS CELL CARCINOMA	45	5	50
WELL DIFFERENTIATED	40	3	43
MODERATELY DIFFERENTIATED	0	1	1
POORLY DIFFERENTIATED	5	1	6
2 ANAPLASTIC CARCINOMA	0	0	0

TABLE 12

RADIOTHERAPY MODALITY ACCORDING TO THE ANATOMICAL REGION OF THE LESION.

MODALITY	GLOTTIC	SUPRAGLOTTIC	TOTAL
KV 250	7	0	7
^{60}Co	37	4	41
	44	4	48

2.17 T.N.M. CLASSIFICATION

All the tumours were re-classified according to the T.N.M. Classification of the UICC 1974 which has been summarized in section 1.17. According to this classification, all tumours were T1 and subclassified as follows.

TABLE 13

	GLOTTIC	SUPRAGLOTTIC	SUBGLOTTIC
T1A	147	21	3
T1B	25	17	0
T1S	5	0	0
	177	38	3

The frequency of nodal metastasis was as follows:

TABLE 14

	GLOTTIC	SUPRAGLOTTIC	SUBGLOTTIC
NO	176	33	0
N1a	0	1	0
N1b	1	1	0
N2a	0	1	0
N2b	0	0	0
N3	0	2	0

According to the revised U.I.C.C. TNM Classification 1978 adopted in 1979, Na and Nb have been subsituted with N. As expected there was only one patient with glottic carcinoma who had nodal metastasis. About 14.2% of all the supraglottic lesions had lymph node metastases some of which were quite advanced. The apparent lack of palpable lymph nodes in those patients with subglottic carcinoma is attributed to the fact that tumours in this region tend to spread to the paratracheal lymph nodes which are deep seated and in most cases inaccessible palpably.

2.18 HISTOLOGICAL DIAGNOSIS

All the patients in this case material had a confirmatory histological diagnosis made from the pre-treatment biopsy material. Table 10 shows the histological distribution of these lesions according to the laryngeal anatomical region. It is evident that 210 (96.3 per cent) were squamous cell carcinomas, 3 (1.3 per cent) were anaplastic carcinomas and 5 (2.4 per cent) were squamous cell carcinomas but as no differentiation was recorded, these were entered as unclassified. That most lesions were squamous cell carcinomas in this case material is consistent with the documented observations. The method used by histopathologists to assess the degree of differentiation of squamous carcinoma is that of an overall impression based on the degree of prickle cell formation, features of keratinization and the overall resemblance of the carcinoma to normal squamous epithelium. On this basis, the lesion is classified into well, moderately or poorly differentiated. This method, while used by most pathologists, has limitations; the subjectivity of the criteria of the differentiation used, the doubts about consistency between observers of the same material and the same observer viewing the material at different times as well as lack of adequate quantitation. While the method of Broders seems to answer the quantitation criticism, counting the cells is impracticable. In this case material, the assessment of the degree of differentiation of the squamous carcinoma was that of an overall impression.

As indicated in table (10) 83.3 per cent of the glottic lesions were well differentiated, 5.8 per cent moderately differentiated and 10.4 per cent poorly differentiated. As regards the supraglottic lesions, 64.7 percent were well differentiated, 17.7 per cent moderately differentiated and 20.6 per cent were poorly differentiated. Again, there is an apparently lower degree of differentiation for the supraglottic lesions in agreement with the documented observations.

The more differentiated the growth, the less likely it is to recurr locally after treatment and to metastasize to lymph nodes and by the blood stream. This assumption is based on the notion that the speed of growth of the tumour and hence its likelihood to metastasize is inversely related to the degree of differentiation. There is some accuracy in this prediction as shown by the work of McGavran and his colleagues (63) who studied the relationship between the degree of differentiation of the primary growth in 96 cases of squamous carcinoma of the larynx to the incidence of lymph node metastasis. The cases of well differentiated squamous carcinoma showed 11 per cent metastasis, the moderately differentiated ones 22 per cent and of the poorly differentiated ones 49 per cent. In this case material, most lesions were well differentiated particularly the glottic lesions of which 83.3 per cent fall into this category. The rate of lymph node metastasis is 1 out of 177, almost insignificant. As for the supraglottic lesions of which 65.7 per cent were well differentiated, the rate of lymph node metastasis was 26 per cent but of course other factors such as the lymphatic drainage of the region must be considered critically.

TABLE 15

HISTOLOGICAL DIAGNOSIS

	GLOTTIC	SUPRAGLOTTIC	TOTAL
1. Squamous Cell Carcinoma	173	34	3
Well differentiated	145	22	2
Moderately differentiated	10	5	0
Poorly differentiated	18	7	1
2. Anaplastic Carcinoma	2	1	0
3. Unclassified	2	3	0

2.19 PRIMARY THERAPY

The patients were divided into three main groups according to the therapy given; primary curative surgery, primary curative radiotherapy and combined radiotherapy and surgery. The group of patients planned for combined therapy were all operated on regardless of the response to the pre-operative radiotherapy. Eight patients were given primary surgical therapy of whom 2 had glottic cancer and 6 had supraglottic cancer. One of the patients with glottic cancer treated by surgery had been treated 20 years previously with radiotherapy for probably tuberculous cervical lymphadenopathy. Table 16 shows the types of surgical procedure given. Most of the patients in this group had supraglottic cancer and were treated by supraglottic laryngectomy and because the frequency of cervical lymph node involvement was higher, we note also a higher frequency of radical neck dissection at the time of the primary surgery.

202 Patients were treated by primary curative radiotherapy. Among these patients 174 had glottic carcinoma, 25 had supraglottic carcinoma and 3 had primary subglottic carcinoma.

21 Patients attended between 1953 and 1965 inclusive were treated by KV 250. The apparatus used was RT 250 Philips machine delivering 15mA. Thoreus fillers 1.5 cm thick were used. The tubes were placed 40 cms from the skin. Doses ranging from 3000-6700 rontgen (2850-6365)rad; conversion factor 0.95) were given in fractionations of 150-200 rontgen (142.5 - 190 rad) per sitting. The field size ranged from 5x5 cm to 6x8 cm.

181 Patients attended between 1966 and 1978 inclusive were treated by the Cobalt 60 machine. Irradiation was administered to the tumour bearing volume using two parallel opposing fields. The field size ranged from 6cm x 8cm to 7cm x 9cm depending on the presence of palpable cervical lymph nodes. In most instances, a total tumour dose ranging from 6000 - 6500 rads was delivered over a period of 6-7 weeks at fractionations of 200 rads per sitting. Table 17 shows the distribution of the patients according to the radiotherapy modality and regional distribution of the lesions.

Until 1971, preoperative radiotherapy was given in doses of 4000 rads at 200 rads fractionations per sitting over a period of 4 weeks; surgery being carried out 4-6 weeks thereafter. An intensive pre-operative radiotherapy policy consisting of 500 rads daily for a period of 5 days (total 2500 rads) and followed immediately by surgery (61) has been introduced and adopted ever since.

All the patients in this combined therapy group, except one, received the intensive pre-operative course on the cobalt 60 machine. The one exception was a patient, treated in the beginning of 1973, who received a total dose of 4000 rads in 4 weeks then operated on 6 weeks subsequently. Table 18 shows the frequencies of the various surgical procedures carried out on these patients.

TABLE 16

FREQUENCY OF PRIMARY SURGICAL PROCEDURE ACCORDING TO THE ANATOMICAL REGION INVOLVED BY THE TUMOUR

PROCEDURE	GLOTTIC	SUPRAGLOTTIC	SUBGLOTTIC	TOTAL
TOTAL LARYNGECTOMY	1	0	0	1
VERTICAL LARYNGECTOMY	1	0	0	1
SUPRAGLOTTIC LARYNGECTOMY	0	5	0	5
SUPRAGLOTTIC LARYNGECTOMY + UNLATERAL NECK DISSECTION	0	1	0	1
	2	6	0	8

TABLE 17

PRIMARY RADIOTHERAPY

	GLOTTIC	SUPRAGLOTTIC	SUBGLOTTIC	TOTAL
KV 250	15	6	0	21
COBALT 60	159*	19**	3	181
	174	25	3	202

TABLE 18

FREQUENCY OF SURGICAL PROCEDURE IN THE COMBINED THERAPY GROUP

PROCEDURE	GLOTTIC	SUPRAGLOTTIC	SUBGLOTTIC	TOTAL
SUPRAGLOTTIC LARYNGECTOMY	0	2	0	2
SUPRAGLOTTICLARYNGECTOMY + HEMITHYROIDECTOMY	0	1	0	1
SUPRAGLOTTIC LARYNGECTOMY + RADICAL NECK DISSECTION	0	1	0	1
TOTAL LARYNGECTOMY + RADICAL NECK DISSECTION	0	2	0	2
	0	6	0	6

* One patient eventually had radical neck dissection

** Also one patient eventually had neck dissection. In both cases the primary was cured by radiotherapy.

2.20 RADIOTHERAPY

To evaluate the relationship between the type of machine used for the radiotherapy treatment and effectiveness in terms of recurrences the patients were divided into two main groups; those treated on the KV 250 machine and those treated on the Cobalt 60 machine. For each group, the doses given were subdivided into three main categories; less than 6000 rad, 6000 rad and more than 6000 rad. Table 19 shows the distribution of the patients according to the type of machine, dosage and the anatomical laryngeal region of the tumour.
Of the 21 patients treated by KV 250 machine, 17 had glottic cancer, 3 had supraglottic cancer and 1 had subglottic cancer. Among these cases three patients with glottic cancer had chronic laryngitis.
The distribution of the patients treated on the Cobalt 60 machine according to the dosage and anatomical laryngeal region is shown on table 19(b).

TABLE 19(a)

KV 250 RADIOTHERAPY

DOSAGE(RAD)	GLOTTIC	SUPRAGLOTTIC	SUBGLOTTIC	TOTAL
< 6000	8 (4)	3 (0)	1 (0)	12 (4)
6000	1 (0)	0 (0)	0 (0)	1 (0)
>6000	8 (3)*	0 (0)	0 (0)	8 (3)
	17 (7)	3 (0)	1 (0)	21 (7)

( ) developed recurrences of whom:

* three in the respective group had chronic laryngeal disease.

TABLE 19(b)

COBALT 60 RADIOTHERAPY

DOSAGE (RAD)	GLOTTIC	SUPRAGLOTTIC	SUBGLOTTIC	TOTAL
< 6000	8 (0)	0 (0)	1 (0)	9 (0)
6000	102 (15)*	16 (3)**	1 (0)	119 (18)
> 6000	47 (6)	6 (1)***	0 (0)	53 (7)
	157 (21)	22 (4)	2 (0)	171 (25)

Among the 171 patients in this group, 157 had glottic cancer, 22 had supraglottic cancer and 2 had subglottic cancer. The corresponding figures for the recurrences in each group and subgroup are indicated for case of comparison. All the doses are in rads after conversion of the rontgen into rad using a conversion factor of 0.95.

( ) indicates the number of patients who developed recurrences of whom:

* 7 patients had chronic laryngeal disease

** 1 patient in this group had chronic laryngeal disease

*** 1 patient in this group had chronic laryngeal disease.

3.00 RESULTS

3.01 SURVIVALS

The survivals for the patients with glottic and supraglottic carcinoma in this case material were calculated using the actuarial method. The three patients with subglottic carcinoma were not included because the number of these patients was too small.

The principle of the actuarial method is as follows:

The probability that a patient will survive, say, n years, is the product of the following probabilities:

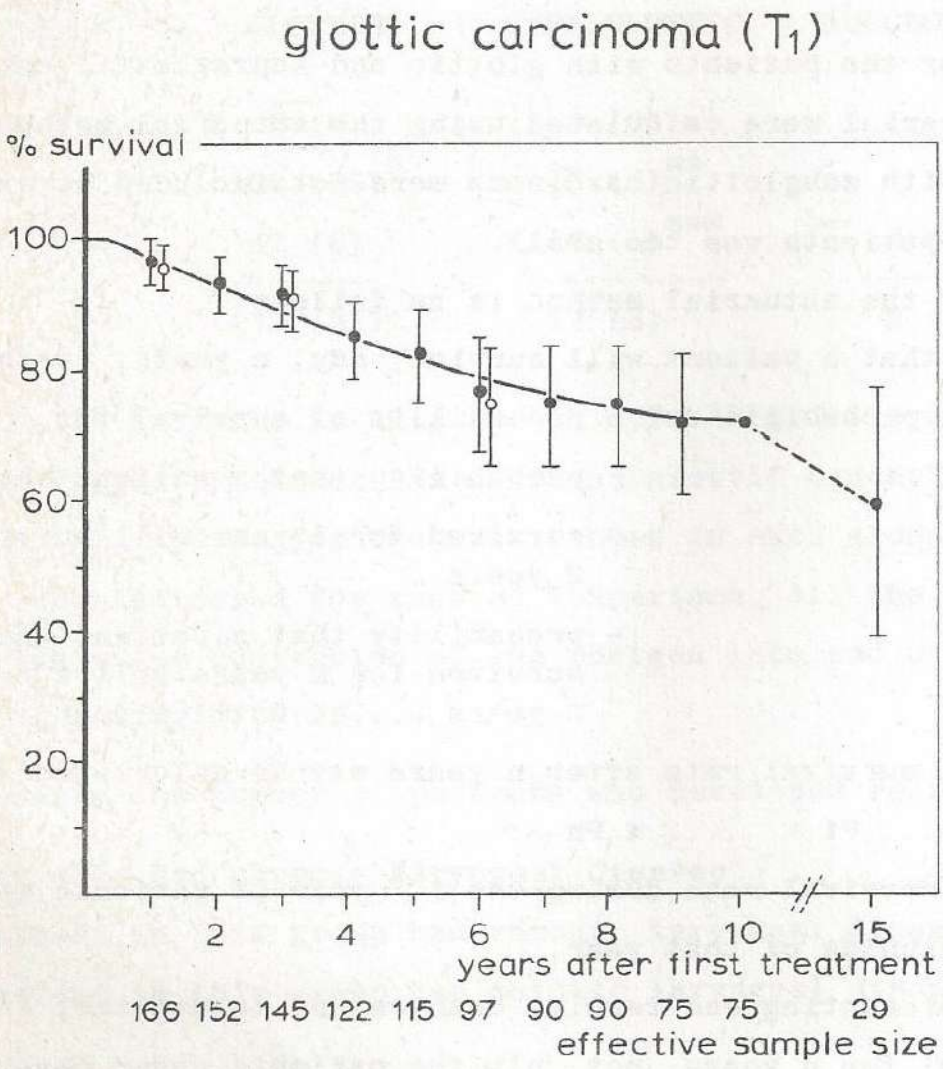
- probability of survival for 1 year
- probability that a patient who has survived for 1 year will survive for 2 years
- probability that a patient who has survived for 2 years will survive for 3 years ..... until n years.

Accordingly this survival rate after n years may be calculated as follows:

$Pn = P1 \times P2 \times .....Pi \times ..... \times Pn$

where Pi is the survival rate during the i^{th} year of patients who were alive at the beginning of that year.

This method of presenting end results enables one to utilize, in calculating survival for n years, not only the patients under observation for a shorter period (64). The Berkson-Gage form (1958) for presenting end results (appendix 2) was used in this case material. The respective data for glottic and supraglottic lesions were entered and the relevant calculations made.


glottic carcinoma (T_1)
% survival
100
80
60
40
20
2
4
6
8
10
15
years after first treatment
166 152 145 122 115 97 90 90 75 75 29
effective sample size

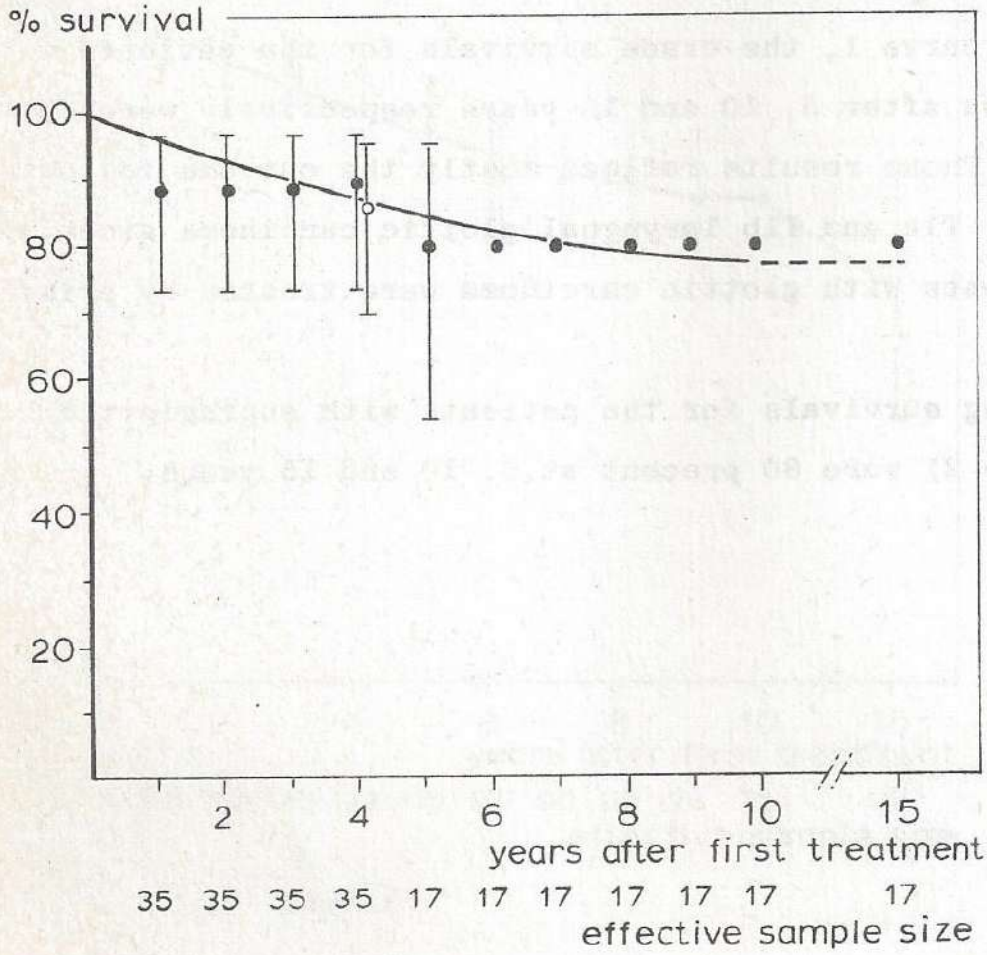
CURVE 1

The survivals were summerized in the form of curves. For the purpose of interpretation, the vertical bars in the survival curves represent 95% confidence limits for the survival concerned. The estimiation of these limits is based on interpolation of binomial tables. This is attested by the "effective sample size" calculated, which indicates the size of a "direct method sample" equivalent to the present sample after a given number of years.

As indicated in curve 1, the crude survivals for the patients with glottic carcinoma after 5, 10 and 15 years respectively were 83, 73 and 60 percent. These results reflect mostly the outcome following radiotherapy for T1a and T1b laryngeal glottic carcinoma since 174 of the 177 patients with glottic carcinoma were treated by primary radiotherapy.

The corresponding survivals for the patients with supraglottic carcinoma (curve 2) were 80 precent at 5, 10 and 15 years.

supraglottic carcinoma (T_1)



CURVE 2

3.02 DEATHS

In this case material, there were 32 deaths during the observation period. 11 Of the deaths were caused by the laryngeal cancer; a mortality rate of 31% while 21 of the deaths were due to causes not related to the laryngeal cancer. This mortality rate of 31% due to disease in a group of cancer patients is very low indeed and compares well with deaths due to natural causes matched by age in the general population. The chance of dying from cancer in this case material is 50% that of dying from other causes. The commonest cause of death in this group of patients was cardiovascular diseases and probably this relates to tobacco smoking. Second primaries ranked the same as the laryngeal cancer (31%) as the cause of death.

TABLE 20

CAUSE OF DEATH

	GLOTTIC	SUPRAGLOTTIC
Deaths due to laryngeal cancer	9	2
Deaths due to other causes	18	3
Myocardial Infarction	6	1
Cerebral vascular Accident	1	1
Cardiac Asthma	1	-
Multiple Myeloma	1	-
Bronchogenic Carcinoma	4	1
Carcinoma Pharynx	1	-
Carcinoma of the colon	1	-
Pneumonia	1	-
Thyrotoxicosis	1	-

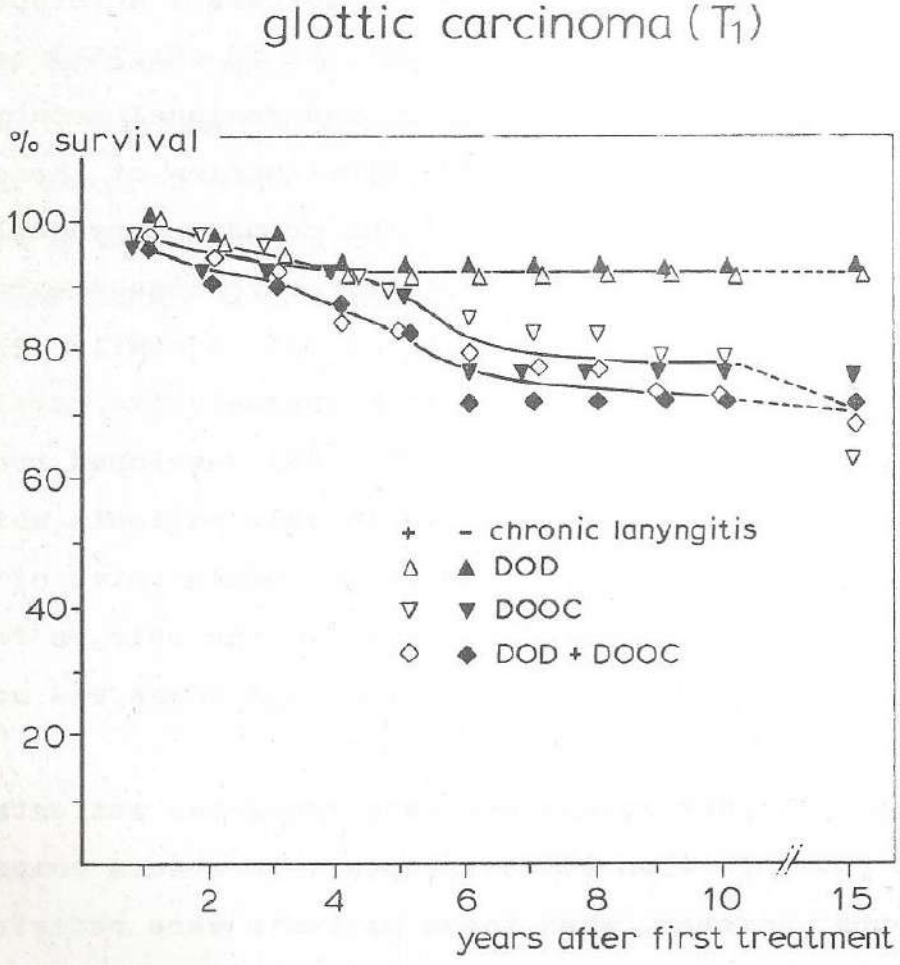
Although there was a significantly high recurrence rate among the patients with chronic laryngeal disease when compared to those without chronic laryngeal disease, we do not note any significant difference in the deaths due to disease in these two groups (X^2=1,47).

Curve 3 shows various types of survival of the glottic cases with and without chronic laryngeal disease. It is evident that no substantial difference in whatever type of survival exsits between these two categories. The only notable difference is that there are more deaths due to other causes (DOOC) than there are deaths due to disease (DOD).

3.03 RECURRENCES

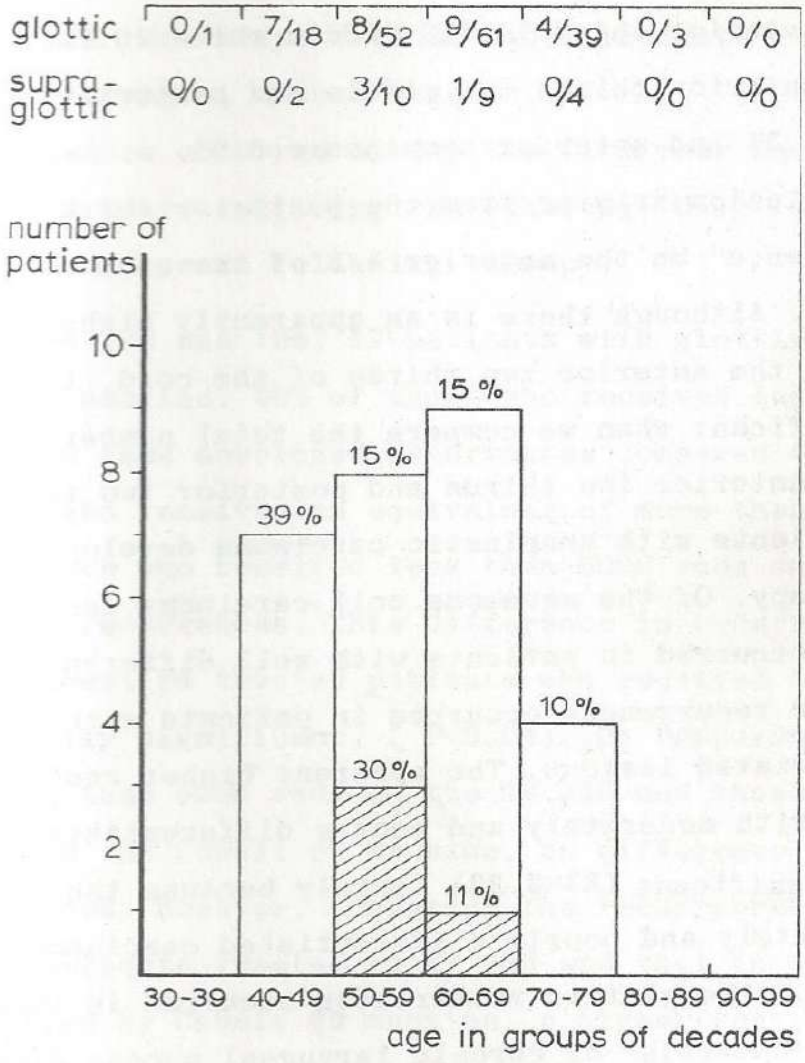
32 of the 202 patients treated by primary radiotherapy developed recurrences; a recurrence rate of 16%. 26 Of the 32 (81.25%) recurrences were local while 6 (18.75%) were both local and regional recurrences. Tables 22-30 summarizes these recurrences. Distribution of these recurrences according to the anatomical region of the primary laryngeal lesion shows that 28 of the 174 patients with glottic carcinoma treated by radiotherapy developed recurrences, a rate of 16%. A similar rate of recurrences is noted for those patients with supraglottic carcinoma treated by radiotherapy of whom 4 out of 25 (16%) developed recurrences. Among the glottic recurrences, 26 occurred in male patients while 2 occurred in female patients. This 13:1 male to female ratio of the patients who developed recurrences is similar to the male to female ratio in the whole material (13:1) indicating that there was no evident sex preponderance.

There is an apparently higher recurrence rate among the patients aged between 40 and 49 years in whom 39% developed recurrences compaired to the other age groups. However, when these patients were redistributed into the KV 250 radiotherapy and Cobalt 60 radiotherapy treated groups, this difference is not statisically significant ($X^2=3.76$). In either group, the peak age incidence of the recurrence (Histogram 4) coincided well with the peak age incedence of the disease in the whole material. 73% of the glottic recurrences were noted on the left vocal cord compaired to only 27% noted on the right vocal cord.


glottic carcinoma (T_1)
% survival
100
80
60
40
20
2
4
6
8
10
15
years after first treatment
+ - chronic lanyngitis
△ ▲ DOD
▽ ▼ DOOC
◇ ◆ DOD + DOOC

CURVE 3

recurrences according to age
(radiotherapy treated)



(%) percentage based on the total number of patients in the age group

glottic local and regional recurrences

supraglottic local and regional recurrences

HISTOGRAM 4

The preponderance for the left vocal cord recurrences is statistically significant ($X^2=4.65$). No tenable explanation is available to explain this discrepancy.

The anatomical site of the primary lesion on the glottis showed recurrence rates as follows: Anterior third 14.3%, middle third 10.7%, posterior third 10.7%, middle and anterior thirds 36% middle and posterior thirds 10.7%, whole vocal cord 14.3% and anterior commissure 3.5%.

One patient with a lesion arising from the posterior third of the cord developed a "recurrence" on the anterior 1/3 of the same cord. This might be a second primary. Although there is an apparently higher recurrence rate for lesions on the anterior two thirds of the cord, this is not statistically significant when we compare the total number of recurrences for lesions on the anterior two thirds and posterior two thirds of the cord.

None of the two patients with anaplastic carcinoma developed a recurrence following radiotherapy. Of the squamous cell carcinoma lesions, 23 (16%) of the recurrences occurred in patients with well differentiated lesions while 4 (40%) of the recurrences occurred in patients with moderately and poorly differentiated lesions. The apparent higher recurrence rate among the patients with moderately and poorly differentiated lesions is not statistically significant ($X2=2.22$) largely because the number of patients with moderately and poorly differentiated carcinoma was too small.

14 Of the 28 (50%) of the glottic recurrences occurred in those patients with long standing anamnesis of chronic laryngeal mucosa disease prior to development of the invasive laryngeal carcinoma. Overall, there were 48 patients with pre-existing chronic laryngeal mucosa disease in the glottic carcinoma material.

These patients had been closely followed up with microlaryngoscopy and microsurgery for periods varying form six months to twenty years when invasive or cytocellular carcinoma was diagnosed histologically. The 29% recurrence rate in those patients with pre-existing chronic laryngeal mucosa disease is statistically significant (X^2=7.38) when compared to the 11% recurrence rate in those patients without a pre-existing chronic laryngeal mucosa disease.
50% Of the recurrences occurred during the first year and 89.3% occurred within the first 2 years following radiotherapy. Only 10.7% of the recurrences were seen 3 years following therapy.

As shown in tables 19a and 19b, 17 patients with glottic cancer were treated by KV 250 machine. 50% of those who received less than an equivalent of 6000 rads developed recurrences compared to 37% recurrence rate among those who received an equivalent of more than 6000 rads. None of the patients who received less than 6000 rads on the Cobalt 60 machine developed recurrences. This difference in recurrence rate among the KV 250 and Cobalt 60 treated patients who received less than 6000 rads is statisically significant, (F=0.04). On comparing the patients who received more than 6000 rads on the KV 250 and those who received an equivalent dose on the Cobalt 60 machine, no difference was noted in terms of recurrences. However, comparing the recurrence rates in the total number of patients treated by KV 250 and that in the total number of patients treated by Cobalt 60 machine, a higher recurrence rate was noted in the KV 250 treated patients (F=0.009).
(F = Fisher's exact probability).

Among the patients who had pre-existing laryngeal mucosa disease and developed recurrence of the tumour following radiotherapy, one patient had the failure attributable to geographical miss in the irradiation field. This patient with a glottic well differentiated squamous cell carcinoma involving the anterior one third or the vocal cord was planned for curative radiotherapy and treated on the Cobalt 60 machine. After receiving a total of 4000 rads, it was discovered that the tumour was geographically out of the irradiation field. Re-adjustment was made and a total of 6000 rads were given. He developed a recurrence two years thereafter and was treated by total laryngectomy.

Understaging was investigated by reviewing the larynx tomograms and laryngograms. Only 23 of the 32 patients had the respective radiographs available. The rest had been destroyed (usually after being stocked for 10 years) or could not be traced. The following radiological criteria were used as radiological evidence of understaging:

1) Obliteration of the Sinus of Morgagni
2) Diminished mobility of the vocal cord
3) Thickening of the ipsilateral ventricular band together with obliteration of the ipsilateral Sinus of Morgagni
4) Obvious tumour extension into the subglottis.

In 15 patients there was no obvious radiological evidence of understaging. Supraglottic extension was noted in 3 cases and subglottic extension was noted in 3 cases of whom one had evident diminution of the mobility of the affected vocal cord.

Interpretation of the radiographs was not possible in two cases; one case had treated pulmonary tuberculosis with traction of the trachea by fibrosis and the other case had severe cervical spine scoliosis with distortion of the trachea including the subglottis. None of the six patients whose lesions were understaged had a pre-existing chronic laryngeal mucosa disease.

TABLE 21

DISTRIBUTION OF RECURRENCES

a) FOLLOWING RADIOTHERAPY

	GLOTTIC	SUPRAGLOTTIC	SUBGLOTTIC
Local	22*/174 (12.7%)	4/25 (16%)	0/3 (0%)
Local + Regional	6** /174 (3.5%)	0/25 (0%)	0/3 (0%)
	28/174 (16.2%)	4/25 (16%)	0/3 (0%)

b) FOLLOWING SURGERY

GLOTTIC	SUPRAGLOTTIC	SUBGLOTTIC
0/2	0/6	0/0

c) FOLLOWING COMBINED THERAPY

GLOTTIC	SUPRAGLOTTIC	SUBGLOTTIC
0/0	0/6	0/3

TABLE 22

RECURRENCES ACCORDING TO SEX

	MALE	FEMALE	TOTAL
GLOTTIC	26	2	28
SUPRAGLOTTIC	4	0	4
	30	2	32

* Three patients developed lung metastases from which they died

** One patient developed pulmonary metastases and is now on chemotherapy palliation.

TABLE 23

RECURRENCES ACCORDING TO THE TNM CLASSIFICATION - RADIOTHERAPY GROUP

	GLOTTIC	SUPRAGLOTTIC
T1aNoMo	20/143	3/21
T1bNoMo	6/25	1/4
T1S	1/5	0/0
T1bN1Mo	1/1	0/0
	28/174	4/25

TABLE 24

LATERALISATION OF THE RECURRENCES

	LEFT	RIGHT	BILATERAL
GLOTTIC	18/72	7/87	3/18
SUPRAGLOTTIC	1/16	2/13	-

S $X_1^2 = 4.65$; left preponderance.

TABLE 25

GLOTTIC RECURRENCES ACCORDING TO THE ANATOMICAL SITE OF THE PRIMARY

ANTERIOR COMMISSURE	1/9
ANTERIOR 1/3	4/30
MIDDLE 1/3	3/15
POSTERIOR 1/3	3/11
ANTERIOR + MIDDLE 1/3	10/44
MIDDLE + POSTERIOR 1/3	3/10
WHOLE CORD	4/55
POSTERIOR COMMISSURE	0/0
	28/174

TABLE 26

GLOTTIC RECURRENCES ACCORDING TO HISTOLOGICAL DIFFERENTIATION OF THE PRIMARY TUMOUR

a) SQUAMOUS CELL CARCINOMA	28/174
WELL DIFFERENTIATED	23/143
MODERATELY DIFFERENTIATED	4/10
POORLY DIFFERENTIATED	1/18
b) ANAPLASTIC CARCINOMA	0/2
c) SQUAMOUS CELL CARCINOMA (Not classified)	0/2

.TABLE 27

TIME RELATIONSHIP BETWEEN RADIOTHERAPY MODALITY AND RECURRENCES

a) SUPRAGLOTTIC (Co^{60})

Duration following R_1	No of Recurrences
< 6 months	1 (25%)
6 - 12 months	2 (50%)
1 - 2 years	1 (25%)
> 2 years	0
	4 (100%) =

b) GLOTTIC LESIONS

	COBALT 60		KV 250		TOTAL
< 6 months	1	(4.6%)	0	(0%)	1
6 - 12 months	12	57.4%	3	(42.9%)	15
1 - 2 years	6	28.6%	3	(42.9%)	9
> 2 years	2	9.4%	1	(14.3%)	3
	21	(100.%)	7	(100%)	28 (174)

( ) indicate the total number of patients treated in each group.

TABLE 28

RADIOTHERAPY DOSE AND RECURRENCES (GLOTTIC LESIONS)

a) KV 250 RADIOTHERAPY

DOSAGE (RAD)	NO OF RECURRENCES
< 6000	4/8
6000	0/1
> 6000	3/8*
	7/17

* Three of the recurrences (all) in this group had chronic laryngeal disease.

b) COBALT 60 RADIOTHERAPY

DOSAGE	GLOTTIC		SUPRAGLOTTIC		SUBGLOTTIC	TOTAL
< 6000	0/8	(0%)	0/0	0%	0/1	0/9
6000	15/102*	(14.7%)	3/16**	(18.8%)	0/1	18/119
> 6000	6/47	(7.8%)	1/6***	(6.3%)	0/0	7/53
	21/157		4/22		0/2	25/171

* 11 Patients in this group had chronic laryngeal disease

** 1 Patient in this group had chronic laryngeal disease

*** 1 Patient in this group had chronic laryngeal disease.

Note that 16 patients had chronic laryngeal disease of whom 14 had glottic cancer and 2 had supraglottic cancer. This constitutes 50% (Table 22) of all the recurrences $X^2 = 7.38$.

3.04 RECURRENCES : THERAPY AND OUTCOME

The course of the patients who developed recurrences is described for each individual patient below; category (a) those with pre-existing chronic laryngeal mucosa disease and category (b) those without pre-existing chronic laryngeal mucosa disease.

a) CHRONIC LARYNGEAL DISEASE GROUP

Case 1.

A 65 years old male who had been on close follow up for hoarseness of voice due to hyperplastic diffuse chronic laryngitis was diagnosed as having invasive squamous cell carcinoma involving the posterior third of the left vocal cord five years later. Histologically, the lesion was poorly differentiated. He received curative radiotherapy on the KV 250 machine. He remained disease free until 2 years and 8 months later when he developed a local recurrence of the disease without evident cervical nodal extension. He was treated by total laryngectomy. The post-operative course was uneventful . He remained free of the laryngeal cancer until 3 years later when he developed bronchogenic carcinoma of the right lung from which he died.

Case 2.

A 54 years old male had a parakeratotic laryngeal disease. A year later, he developed a well differentiated invasive squamous cell carcinoma involving the whole of the left vocal cord.

He was treated by a curative course of radiotherapy on the KV 250 machine. He was noted six months later with a local recurrence of the disease for which he was treated by total laryngectomy. He has remained free from disease for now 12 years. He is still on follow-up.

CASE 3

A male aged 67 years was on follow-up for a leukoplakic lesion on the anterior one third of the left vocal cord for a year when biopsy revealed a histological picture consistent with carcinoma in situ. He received a curative course of radiotherapy on the KV 250 machine. He remained disease free until 2 years later when he developed a localised recurrence for which he was treated by total laryngectomy. A year later he developed cervical lymph node metastases on the left side and he was treated by a radical neck dissection. Since then the patient has remained disease free and still on follow-up for now 14 years.

CASE 4

A 75 years old male with leukoplakia on the whole of the left vocal cord developed an infiltrative well differentiated squamous cell carcinoma six months after the initial biopsy. He received a curative course of radiotherapy on the KV 250 machine. 8 Months later, he developed a local recurrence for which he was treated by a laryngofissure and cordectomy. He remained disease free until 14 years thereafter when he died of a cerebrovascular accident.

CASE 5

A 57 years old male who was on follow-up for leukoplakia of the left ventricular band developed an invasive well differentiated squamous cell carcinoma 4 years later. He was treated by a curative course of radiotherapy on the Cobalt 60 machine. Seven months later, he developed a local recurrence for which he was treated by total laryngectomy. Since then he has remained disease free and still on follow-up for now 4 years.

CASE 6

This was a 65 years old male who was on follow-up for acanthosis and parakeratosis of the left ventricular band. He developed an invasive well differentiated squamous cell carcinoma at the same site 10 years later. He received a curative course of radiotherapy on the Cobalt 60 machine. He remained locally disease free until 2 years later when he developed a local recurrence. He was treated by total laryngectomy and ever since he has remained free from disease for now 5 years. He is still on follow-up.

CASE 7

A 62 years old male on follow-up for leukoplakia involving the anterior 2/3 of the left vocal cord developed a well differentiated squamous cell carcinoma six months later. He was curatively treated by radiotherapy on the Cobalt 60 machine. Six months thereafter, he developed a local recurrence and was treated by total laryngectomy. Five months thereafter he developed a stomal recurrence which was treated by surgical excision.

For the subsequent two years he was on follow up, this patient was disease free. He has been lost to follow up. No pre-operative tracheostomy had been done on this patient. The stomal recurrence could be explained by tumour cell implantation at the time of surgery or subglottic extension of the tumour which was therefore probably understaged.

CASE 8

A 57 years old male with diffuse hypertrophic mucosa over the anterior 2/3 of the left vocal cord developed an infiltrative well differentiated squamous cell carcinoma after 6 months of follow up. He received a full course of curative radiotherapy on the Cobalt 60 machine. 8 Months later he developed a local recurrence and was treated by total laryngectomy. He is alive and well for 5 years now.

CASE 9

A 46 years old male on follow up for hyperkeratotic lesion involving the left posterior 2/3 of the cord developed an infiltrative well differentiated squamous cell carcinoma two years later. He was treated by a full curative course of radiotherapy on the Cobalt 60 machine. 8 Months later, he developed a recurrence at the initial site of the tumour. He was treated by laryngofissure and cordectomy and has remained alive and well for now 4 years thereafter.

CASE 10

A 55 years old male on follow up for squamous hyperplasia involving the anterior two thirds of both vocal cords developed a poorly differentiated squamous cell carcinoma one year later. A curative course of radiotherapy on the cobalt 60 machine was given. A year later he developed a local recurrence and treated by total laryngectomy. Two years after the total laryngectomy he developed a right upper lobe bronchogenic carcinoma for which he was treated by thoracotomy and pneumonectomy. He has remained free from the laryngeal and bronchogenic carcinoma and is still on follow up for 5 years now.

CASE 11

This was a 76 years old male on follow up for hyperkeratosis involving the anterior 2/3 of the right vocal cord. He developed a poorly differentiated squamous cell carcinoma after 2 years and was given a full course of radiotherapy on the Cobalt 60 machine. He developed a local recurrence 3 years later and was treated by hemilaryngectomy. For the subsequent 5 years he has been on follow up, he remains disease free.

CASE 12

This was a 60 years old male on follow up for diffuse hyperplasia and parakeratosis involving the whole length of both vocal cord. He developed a well differentiated squamous cell carcinoma 5 years later then was treated by a full course of radiotherapy on the Cobalt 60 machine. He remained free from disease until 4½ years later when he developed local recurrence

with nodal metastases and was treated by total laryngectomy with right sided radical neck dissection. Subsequently, he has remained disease free and is still on follow up for 7 years now.

CASE 13

A 66 years old male on follow up for diffuse squamous hyperplasia affecting both anterior 2/3 of the vocal cords developed a well differentiated squamous cell carcinoma 7 years later. He received a curative course of radiotherapy on the Cobalt 60 machine. 1½ Year later, he developed a local recurrence for which he was treated by total laryngectomy. He remained locally disease free but developed lymph node metastases on the right side. This was treated by radical neck dissection. At the time of this write up, the patient is on methotrexate chemotherapy palliation. This case is a typical example of a very aggressive disease which despite early diagnosis and appropriate therapy remains unmanageable.

CASE 14

Was a 46 years old female on follow up for squamous cell hyperplasia affecting the whole length of the left vocal cord. She developed an invasive well differentiated squamous cell carcinoma one year later and was treated by a full course of radiotherapy on the Cobalt 60 machine. One year later, local recurrence was noted and she was treated by total laryngectomy. She remains alive and disease free now 6 years subsequent to the laryngectomy.

CASE 15

This was a 49 years old male on follow up for leukoplakia and parakeratosis involving both anterior 2/3 of the vocal cords. He developed an invasive well diferentiated squamous cell carcinoma three years later. A full course of radiotherapy on the Cobalt 60 machine was given. He remained locally free from disease but died a year later of disseminated pulmonary metastases. This case like case 14, is another example of a very aggressive disease.

CASE 16

Was a 68 years old male with leukoplakia affecting both vocal cords for 6 years when biopsy revealed a well differentiated squamous cell carcinoma. He received a full course of radiotherapy on the cobalt 60 machine. He remained disease free until after two years when he developed local recurrence, airway obstruction and died before treatment could be instituted.

(b) RECURRENCES: NO CHRONIC LARYNGITIS

CASE 1

This was a 42 years old male with a well differentiated squamous cell carcinoma involving the anterior commissure. He was treated by a full course of radiotherapy on the Cobalt 60 machine. For the subsequent one year and 8 months he remained disease free. Thereafter, he developed a local recurrence and treated by hemilaryngectomy. After 1 year 4 months following surgery, he developed another local recurrence and was treated by total laryngectomy. This patient died four years later due to disseminated pulmonary metastases while locally free from disease.

CASE 2

A 65 years old male had a well differentiated squamous cell carcinoma involving the whole of the right vocal cord. He received a full course of radiotherapy on the cobalt 60 machine. One year and two months later, he developed a local recurrence with cervical lymph node metastases on the right side. A laryngectomy with unilateral radical neck dissection was done. The patient remained free from local and regional disease but died after one year of myocardial infarction.

CASE 3

This was a 46 year old male with a well differentiated squamous cell carcinoma involving the posterior 1/3 of the right vocal cord. He was treated by a full course of radiotherapy on the KV 250 machine. Eight months later, local and regional recurrences were noted. A total laryngectomy and radical neck dissection on the right side was done. He has remained free from disease for now 14 years.

CASE 4

Was a 73 years old male with a poorly differentiated squamous cell carcinoma arising from the whole of the left vocal cord. A full course of radiotherapy on the Cobalt 60 machine was given. A local recurrence noted 11 months later was treated by a hemilaryngectomy. He has remained free from disease for now 5 years.

CASE 5

This was a 57 year old male with a well differentiated squamous cell carcinoma arising from the anterior 2/3 of the left vocal cord. He was treated by a full course of radiotherapy on the Cobalt 60 machine. 8 Months later, a local recurrence was noted and treated by total laryngectomy. He has remained free from disease for now 14 years.

CASE 6

A 73 years old male with a poorly differentiated squamous cell carcinoma involving the anterior commissure. Following a full course of radiotherapy on the Cobalt 60 machine, he developed a local recurrence 4 months later. A total laryngectomy was done. Five months thereafter, he developed lymph node metastases on the right side for which he was treated by radical neck dissection. He remains free from local and regional disease for now 2 years following therapy. This patient had bronchogenic carcinoma and treated by left upper lobectomy 4 years before he developed the laryngeal carcinoma. No evidence of the bronchogenic carcinoma noted until now.

CASE 7

This was a 67 years old male who 4 years earlier had a bronchogenic carcinoma involving the right upper lobe and curatively treated by lobectomy. He developed a well differentiated squamous cell carcinoma of the anterior two thirds of the right vocal cord and received a full course of radiotherapy on the Cobalt 60 machine. A year thereafter, he developed a local recurrence and was treated by total laryngectomy. He is alive and well now 3 years thereafter.

CASE 8

A 52 years old male with a well differentiated squamous cell carcinoma involving the anterior 1/3 of the left vocal cord. He received a full course of radiotherapy on the Cobalt 60 machine. 1 Year and 9 months later, he developed a local recurrence for which he was treated by a total laryngectomy. He remains alive and free from disease for now 10 years.

CASE 9

46 Years old male with a well differentiated squamous cell carcinoma involving the posterior 2/3 of the left vocal cord. He was treated by a full course of radiotherapy on the Cobalt 60 machine. 1 year and 1 months later, he developed a local recurrence and treated by hemi-laryngectomy. 1 Year and 5 months later he developed another local recurrence for which total laryngectomy was done. 6 months later, he developed a stomal recurrence and died of massive bleeding.

CASE 10

This was a 59 years old male with a well differentiated squamous cell carcinoma involving the whole of the right vocal cord. He received a full course of radiotherapy on the Cobalt 60 machine. 7 Months later he developed a local recurrence for which he was treated by a laryngofissure and cordectomy. Another local recurrence noted 5 months after the cordectomy was treated by a vertical hemilaryngectomy. Subsequently, the patient has remained free from disease for now 4 years.

CASE 11

This was a 52 years old male with a squamous cell carcinoma (differentiation not indicated) involving the middle third of the right vocal cord. He received a full course of radiotherapy on the cobalt 60 machine. 1 Year and 5 months subsequently, he developed a local recurrence and was treated by total laryngectomy. 2 Years and 1 month later he developed lymph node metastases on the right side and was treated by a radical neck dissection. He has ever since remained alive and free from disease for now 7 years.

CASE 12

This was a 51 years old man who had a right nephrectomy for hypernephroma 6 years prior to the laryngeal complaints. He had an epiglottic wel- differentiated squamous cell carcinoma for which he received a full course of radiotherapy on the cobalt 60 machine. 10 Months later, he developed a local recurrence which was treated by total laryngectomy. Since then he has remained disease free and is now on follow up for 4 years.

CASE 13

This was a 57 years old male who had a poorly differentiated squamous cell carcinoma involving the epiglottis. He was treated by a full course of radiotherapy on the cobalt machine. 4 Months later he developed a local recurrence for which he was treated by total laryngectomy. He has remained well and disease free for now 4 years.

CASE 14

This was a 60 years old male with a well differentiated squamous cell carcinoma involving the posterior 2/3 of the left vocal cord. He received a full course of radiotherapy on the cobalt 60 machine. A local recurrence was noted 2 months after the completion of the radiotherapy. A total laryngectomy was done. Thereafter, he remained locally disease free until 4 years later when he developed multiple lung metastases from which he died.

CASE 15

This was a 42 years old female with a well differentiated squamous cell carcinoma involving the posterior third of the left vocal cord. She was treated by a full course of radiotherapy on the KV 250 machine. 1¼ Year later, a local recurrence was noted. She was treated by a total laryngectomy. She has remained free from disease for now 16 years.

CASE 16

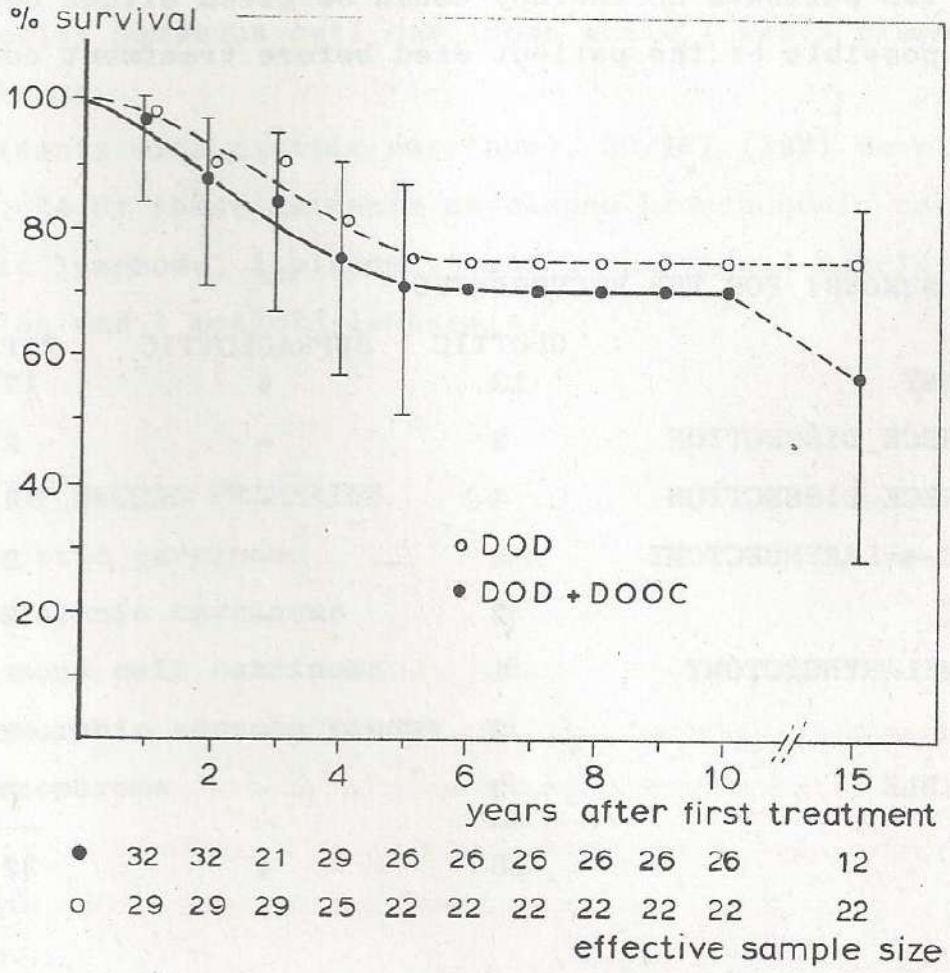
This was a 63 years old male with a well differentiated squamous cell carcinoma arising from the anterior 2/3 of the left vocal cord. He received a full course of radiotherapy on the KV 250 machine. 1 year and 7 months later, a local recurrence was noted and total laryngectomy was done. He has remained free from disease for now 15 years.

In summary, there were two deaths due to the disease in the group of patients who developed recurrences in the chronic laryngeal disease group; patient number 15, who died of disseminated pulmonary metastases and patient number 16 who died of acute airway obstruction. The patient number 7 might be dead of the stomal recurrence. The patient number 13 is still on chemotherapy for the pulmonary metastases but the outcome is definitely lethal. Two patients died of causes unrelated to the disease; patient number 4 who died of cerebrovascular disease and patient number 1 who died of bronchogenic carcinoma.

Among the patients who developed recurrences but devoid of pre-existing chronic laryngeal disease, two patients died of the disease of whom patient number 1 died of pulmonary metastasis while locally free from disease and patient number 9 who died of bleeding from a stomal recurrence. Two patients had second primaries; patient number 6 who developed a bronchogenic carcinoma and patient number 12 who had a hypernephroma prior to the development of the laryngeal cancer.

The survivals for the patients after salvage surgery is shown below. Excluding those patients who died of other causes, there are 26 patients successifully controlled. This gives a salvage rate of 81.25% (26/32). From the survival curves 1 and 4 it is clear that there is no difference between this group of patients who were surgically salvaged following the recurrence and those who did not develop recurrences following radiotherapy. The mortality rate of 18.75% in this group of recurrent cancer patients is very low indeed and compares well with deaths in the general population within the same age group.

glottic carcinoma (T_1)
recurrences



CURVE 4

The second primary rate in this group is 12.5% of which 75% were bronchogenic carcinomas and 25% abdominal visceral malignancies. A similar rate of second primaries is noted (12.9%) for the whole case material. Table 31 summerizes the surgical procedures utilised to salvage the patients who developed recurrences. It is notable that over 75% of all the patients eventually lost their larynges. Attempts at conservative surgery failed on two occasions and resort to total laryngectomy made. Only in 5 patients was conservative surgery adequate in controlling the disease. In two patients no therapy could be given either because surgery was not possible or the patient died before treatment could be effected.

TABLE 29

TYPE OF SALVAGE SURGERY FOR THE RECURRENCES

	GLOTTIC	SUPRAGLOTTIC	TOTAL
TOTAL LARYNGECTOMY	13	4	17
LARYNGECTOMY + NECK DISSECTION	2	-	2
LARYNGECTOMY → NECK DISSECTION	4	-	4
HEMILARYNGECTOMY → LARYNGECTOMY	2	-	2
HEMILARYNGECTOMY	2	-	2
CORDECTOMY → HEMILARYNGECTOMY	1	-	1
CORDECTOMY	2	-	2
NO THERAPY POSSIBLE	2	-	2
	28	4	32

3.05 SECOND PRIMARIES

25 Of the 218 patients with laryngeal carcinoma studied had concurrent or developed second primary malignancies later. This gives a frequency rate of 12.9%.

Of the patients with supraglottic carcinoma 8/38 (21%) developed second primaries of which one was concurrent with the laryngeal malignancy. Out of these, 7/8 (87.5%) developed bronchogenic carcinoma and one patient (12.5%) had a hypernephroma. 6 Of the bronchogenic carcinomas were histologically squamous cell carcinoma while 1 was a pleomorphic adenocarcinoma.

Of the patients with glottic carcinoma, 20/177 (12%) developed second primaries. 14 Of these patients developed bronchogenic carcinoma, 1 histiocytic lymphoma, 1 plasmacytoma, 1 pharyngeal carcinoma, 2 carcinoma of the colon and 1 myeloid leukaemia.

TABLE 30

FREQUENCY OF SECOND PRIMARIES

a. Supraglottic carcinoma	8
- Bronchogenic carcinoma	7
Squamous cell carcinoma	6
Pleomorphic adenocarcinoma	1
- Hypernephroma	1

b) Glottic Carcinoma

- Bronchogenic Carcinoma	14
Squamous cell carcinoma	10
Anaplastic carcinoma	4
- Histiocytic lymphoma	1
- Multiple Myeloma	1
- Pharyngeal carcinoma	1
- Adenocarcinoma	
- Rectum	1
- Sigmoid colon	1
- Myeloid Leukaemia	1
	20

3.06 COMPLICATIONS

No complications were noted among the patients treated by primary surgery and a combination of radiotherapy and surgery.
59% of the patients treated by radiotherapy developed complications of which (2/202)or 1% were major comlications and 99% were minor complications. For clarity, a major complication is that which necessitates admission for management or temporary withdrawal of the radiotherapy until the patient can tolerate further irradiation. The complications noted did not show any relationship with the dose of radiotherapy administered, that is, the frequency of their occurrence among the patients who received less than 6000 rad was similar to that in those patients who received more than 6000 rad. The frequency of mucositis and oedema among those patients who were treated by Cobalt 60 was significantly higher than among those patients treated by KV 250 ($X_1^2 = 19.83$)*. Similarly, there was a significantly high rate of epidermolysis among the KV 250 treated patients compared to those who were treated on the Cobalt 60 machine. ($X_1^2 = 6.74$). Notable is the subtantically low incidence of sicca syndrome of the upper aerodigestive tracts. Among the major complications noted were severe mucositis and radiochondronecrosis of the larynx and trachea.

* Table 31

Both these patients were treated by the KV 250. One patient developed a severe mucositis and oedema of the pharyngolarynx which necessitated stoppage of therapy and admission for treatment with nasogastric tube feeding, prednison and tetracycline. The other patient was a 65 years old male with T1NoMo glottic carcinoma who received 5500 rad on the KV 250 machine at 200 rad fractionations per sitting. During the period of the radiotherapy, he developed a moderately severe mucositis which settled with muthesa topical therapy. He remained free of disease until after 10 months when he was acutely admitted with airway obstruction due to radionecrosis of the larynx and trachea. This patient has been on permanent tracheostomy todate.

TABLE 31.

DISTRIBUTION OF THE COMPLICATIONS ACCORDING TO THE TYPE OF RADIOTHERAPY

	KV 250	COBALT 60	TOTAL
MUCOSITIS AND OEDEMA	3	80	83
EPIDERMOLYSIS	11	19	30
SICCA SYNDROME	2	4	6
RADIOCHONDRONECROSIS	1	0	1
	17	103	120

4.00 GENERAL DISCUSSION

Radiotherapy is now the accepted treatment of choice for early (T1 and T2) laryngeal carcinoma (49). While the majority of the patients thus treated are cured, recurrences or failures are reported in various series. Miller, A.H. (81) noted that 42% of the 43 patients with carcinoma in situ treated by radiotherapy developed recurrences. On the basis of this result he recommended radiotherapy for only extensive lesions or those lesions involving both vocal cords.
Bertil Martensson (28) noted a recurrence rate of 22% in his series of 176 T1 laryngeal carcinoma patients. Similar results have been documented by other authors (72, 82, 83, 85, 81, 88, 89). In this study, the recurrence rate among the radiotherapy treated patients is 16% for the glottic and supraglottic carcinoma lesions respectively.
Fletcher, G.H. (86) indicated that the reasons for irradiation failure in squamous cell carcinoma of the larynx were:

(I) : Geographical miss

(II) : Specific extension of the tumour with an unfavourable tumour bed.

(III) : Low dosage for the volume of the tumour

(IV) : Poor technique or techniques which do not ensure daily coverage of the tumour

(V) : Sigmoid response curve: 85% control of T1 glottic tumours and 90% control of T1 and T2 supraglottic tumours.

(VI) Occurrence of second primaries which might account for the 25% of the so called recurrences on the vocal cord. In the present study there was only one geographical miss among the recurrences and in this case the patient was successfully salvaged by surgery when the recurrence was noted. When reviewing the radiographs of the patients with local recurrences, 6 cases were considered understaged in this study. Of these three had tumour extension beyond the glottis (supraglottic or subglottic extensions) without cord fixation and three had radiological evidence of diminished movements of the vocal cord. According to the TNM classification (48) all these six cases qualify for T2 stage. Since the dose cure curve for T1 and T2 glottic cancer is the same (75) low dosage cannot account for the failures in these cases. Higher recurrence rates were noted in those patients who received less than 6000rads on the KV 250 machine compaired to those who received a similar dose on the cobalt 60 machine. This difference is not evident in the cases which received larger doses on either machine. While low dose would explain the recurrences in these patients who received less than 6000 rads, it would be expected that similar recurrence rates would obtain for those cases treated on the KV 250 and Cobalt 60 respectively. All parameters constant, it is evident from this study that low doses on the KV machine increases the risk of recurrences. Only one patient was considered to have developed a second primary in the region of the original tumour in this series. This was a patient initially with a lesion involving the posterior third of the cord and two years following radiotherapy developed a lesion on the anterior third of the same cord. In all the other cases, the recurrences occurred at the same site as the original lesion.

The anatomical site of the lesion on the vocal cord has been incriminated as relating to the outcome following radiotherapy in laryngeal carcinoma. Lederman (26) pointed out that for lesions involving the dorsal surface and free margin of the cord, response to radiotherapy was better. He ascribed lesions involving the inferomedial surface of the cord with relatively poor response to radiotherapy. Likewise, early lesions involving the middle third of the vocal cord have been shown to have the best prognosis following treatment by radiotherapy (90-95) while lesions involving the posterior third of the vocal cord have the worst prognosis in terms of recurrences, poor response to radiotherapy and late metastasis following radiotherapy. Some workers have recommended such lesions for primary surgery in favour of radiotherapy (98). Controversy centres on lesions involving the anterior third of the vocal cord and extending on the anterior commissure.

Kirshner, J.A. (96) noted failure rates of up to 60% following radiotherapy. On this premise, such lesions have been recommended for partial of total laryngectomy instead of primary radiotherapy. Richard H. Jesse et al (87) comparing the results of radiotherapy of vocal cord cancer with and without anterior commissure involvement noted that T1 lesions had recurrence rates of 8,4% when the anterior commissure was involved and 12,8% when the anterior commissure was not involved.

Regarding T2 tumours the recurrence rates were 25% and 20% respectively. From this study it is obvious that it is only the lesions with extension outside the glottis and involving the anterior commissure that do not respond favourably to radiotherapy. The anatomical site of the lesion on the vocal cord did not have any influence on the recurrences in the present study. The observed apparently high recurrence rates for lesions involving the anterior two thirds of the vocal cord, was not statistically significant. This result is in agreement with the findings of Richard H. Jesse et al (87) and is in accordance with what would be expected. For well staged T1 laryngeal glottic carcinoma, the lesion is superficial and there should be no difference in response to radiotherapy regardless of the anatomical site on the vocal cord.

Several workers have reported poor response to radiotherapy in early glottic carcinoma arising in precancerous lesions. Lederman (26) indicated that precancerous lesions including papillomatosis, leukoplakia and hyperkeratosis could adversely affect response to radiotherapy. Jean-Claude Harriot et al (88) in an analysis of the causes of failures in early vocal cord cancer noted that 50% of the patients with failure had initial leukoplakia. The findings in the present study confirm the latter observations. 50% (14 out of 28) of the glottic recurrences occurred in patients with a pre-existing chronic laryngeal mucosa disease prior to the development of the laryngeal carcinoma. In none of these failures was attributable to geographical miss or understaging.

This correlation between pre-existing chronic laryngeal mucosa disease and failure of control of the laryngeal carcinoma was statistically significant (X^2=7.38). This result indicates that the chances of a glottic laryngeal carcinoma arising from a leukoplakia or any other pre-existing chronic laryngeal mucosa disease being cured by primary radiotherapy are 50%..The remainder 50% will develop recurrences and hence require salvage surgery. On this premise, such patients are best treated by surgery primarily or when radiotherapy is used, a close follow up on these patients must be done to ensure that recurrences are picked up on time and treated surgically. Whereas in a majority of early glottic carcinoma patients treated by radiotherapy the voice is preserved, those patients with pre-existing chronic laryngeal disease have 50% chance of retaining a normal voice.

We note a remarkably high recurrence rate for lesions on the left vocal cord when compared to lesions on the right vocal cord. This predominance in left vocal cord recurrences cannot be explained by geographical miss, chronic laryngeal mucosa disease or any technical fault in the administration of the radiotherapy. Further observations are recommended.

According to J.E.Till et al (62), the bulk of treatment results for cancer of the larynx from different centres are essentially comparable in that the crude five year survival rates for all glottic and supra-glottic cases were not strongly correlated with the type of primary therapy used. There was no notable improvement in the crude or actuarial survival rates during the period under review (1955-1971) and there was no tenable explanation forthcoming regarding this constant result.
In an excellent review of the role of radiotherapy in cancer of the larynx with relationship to the TNM-system of staging, Vermund, H. (49) found out that the five year survivals among patients treated by radio-therapy was 78 percent compared to 83 percent of the patients receiving primary surgical therapy. In the present study, the glottic cancer cases were mainly treated by radiotherapy. Survivals at 5, 10 and 15 years were 83, 73 and 60 percent respectively.
However, these are actuarial survivals and although comparatively higher than those noted by Vermund, they cannot be claimed to be superior.
The survivals for those patients who were treated primarily by surgery in the present study was 100%. Apart from the number of cases so treated being too small for statistical comparison, these patients constitute a selected group. Vermund noted that T1No supraglottic carcinoma lesions are readily curable by radiotherapy with an absolute five year survival of 65% and relative survival of 73%.

These results compared favourably with the 59% and 71% respectively for lesions treated primarily by surgery. In the present study, the survivals for the supraglottic carcinoma lesions was 80 percent at 5, 10 and 15 years respectively. While this is the result of radiotherapy together with combined radiotherapy and surgery treatment, and aware that the type of primary therapy used does not influence the outcome (62) these survival rates are remarkably good. The sample size of the supraglottic carcinoma case material was effective for statistical analysis.

It is remarkable that the survival at 5-years in the recurrence cases is only slightly lower than in all the cases and even then this difference is not statistically significant ($X^2 = 2.26$). However when we exclude the patients who died of other causes (i.e. measured by dead due to disease only) a significant difference ($X^2 = 7.57$) is apparent. It is pertinent from this finding that the salvage rate of 81.25% was quite satisfactory and compares very well with that noted by other authors for T1 lesions (82, 84, 85) if not superior in some cases. The mortality rate due to the laryngeal carcinoma (both glottic-31% and supraglottic-29%) is very low indeed. This mortality in a group of cancer patients compares favourably with the mortality rate in the general normal population matched by age. This means that in early laryngeal cancer, adequate therapy can offer an excellent result. Chronic laryngeal disease adversely influences the outcome of radiotherapy

in early laryngeal carcinoma as far as recurrences are concerned. The chance of cure in these cases when thus treated is 50% according to the present study. However, with meticulous follow up, these recurrences can be detected early and appropriately salvaged by surgery with excellent outcome. Conservative salvage surgery has not been effective in this case material. 75% of the patients who developed recurrences in the group of chronic laryngitis patients eventually lost their larynges. On the basis of this result, recurrences of laryngeal carcinoma in patients with pre-existing chronic laryngeal disease are best salvaged by total laryngectomy. Definitely a palicy of primary radiotherapy for early laryngeal carcinoma in patients with chronic laryngeal disease presupposes a close follow up. Where facilities are inadequate (economical, social or otherwise) primary surgery in such cases should be seriously considered.

Occurrence of multiple primaries as noted in this study has been recognized for now over a century. Bilroth (65) documented the first case of multiple primaries in 1860. Since then, numerous series have been reported in the medical literature with incidences varying from 1%-16% (66-75). This observation is in agreement with the findings in the present study in which 28 of the 218 patients studied developed a second primary - an incidence of 12.9%. According to Warren and Grates (76) a person with one cancer is 11 times more prone to develop a second malignancy compared to a patient in whom the cancer has not developed.

Marcus Brown (70) examined the incidence of second primaries in radiotherapy treated laryngeal carcinoma subjects. He noted that 61 of the 1600 patients (3.8%) developed second primaries with a male preponderance. 64.2% of the second primaries in those patients with supraglottic carcinoma occurred in the lungs while only in 20% was the lung the site of the second primary in those patients with glottic carcinoma.

The male preponderance in the incidence of second primaries in the present study conforms to these findings. However, there is no significant difference in the occurrence of second primaries on comparing the supraglottic and glottic carcinoma patients, 87.5% of the second primaries in those patients with supraglottic carcinoma occurred in the lungs while 70% was the rate for the same site in those patients with glottic carcinoma.

Marcus Brown (70) noted that only one second primary occurred within the radiotherapy field. Two of the second primaries in his series occurred in the penumbra of irradiation. The patients in the study were followed up for a maximum of 10 years following therapy. Lawson and Soms (77) reported an incidence of 5,6 % laryngeal second primaries in a material of 535 patients followed up 5-25 years after treatment of cordal (T1A and B) carcinoma. Striking was the observation that the rate of second primaries in the larynx was significantly higher in the radiotherapy treated patients (9%) when compared to the surgically treated patients in whom the rate was only 3.9%. The patients in the present study were followed up for 1-15 years. Only one second primary was noted within the irradiation field in the radiotherapy treated patients and even then, the second primary was noted two years following therapy. While the period of follow up was shorter than was the case in Lawson et al's series, if more second primaries within the laryngopharynx were to develop, this would have been apparent. Moertel et al (66) noted that 50% of the second primaries showed up within the subsequent 6 months following treatment.

There has so far been no clear reason why multiple primaries develop in a given individual. The so far noted strong association between supraglottic/hypopharyngeal carcinoma and second primaries in the lungs (67,68,72,73) relate to a common aetiological factor. Heavy tobacco smoking and spirituous alcohol ingestion are aetiologically associated with carcinoma of the supraglottis/hypopharynx and lung. Since the majority of these patients with laryngeal carcinoma are heavy smokers or

heavy drinkers or both, there is a possibility of a common carcinogen responsible for lung cancer and laryngeal cancer; afterall, all these sites share a common pathway for inhaled chemicals. While this theory may explain the occurrence of laryngeal and lung cancer in a given subject, still it fails to justify the occurrence of second primaries elsewhere in the body. There seems to be a possible high susceptibility to cancer in some individuals and this may relate to a breakdown in the body immune defence mechanism.

Lawson and Soms (77) have suggested that radiation induced carcinogenesis particularly with supervoltage directed to the laryngeal mucosa may have a role to play in the induction of second primaries within the larynx Accumulating evidence indicates that in head and neck cancer impaired cellular immunity can be found in the early stages (79). If, as suggested (80) cell mediated immunity serves a "surveillance" function to eliminate "forbidden clones" of malignant cells, in impaired immunity and in the presence of one primary, the immunologically relatively incompetent subject is quite likely to develop another primary.

Second primaries induced by radiotherapy are diagnosed purely by association since there is no clinical, radiological or histological way of distinguishing these neoplasms from others. Evidence based on observations of patients treated for thyrotoxicosis and tuberculous lymphadenitis with radiotherapy has indicated that the mean interval

in radiation induced tumours of the pharynx is 25.5 years (78). Should this be true, then the patient who developed a second primary in the pharynx at 2 years in this study can hardly be considered as radiation induced. The duration of 15 years follow-up in these cases falls far short of the observed period for development of radiotherapy induced tumours.

The significance of second primaries in laryngeal cancer patients stems on the prognosis. 21.7% of all deaths in the present study were caused by second primaries. At the time of death, all these patients had their cancer locally controlled. Similar observations have been made by other authors (69, 70, 73, 84). This stresses the need for a thorough otorhinolaryngological and systematic appraisal of all patients with laryngeal cancer for possible concomitant primaries as this will have a major influence on the plan of therapy. A well planned regular follow-up will enhance early detection of these second primaries.

5.00 GENERAL CONCLUSIONS

1. In early laryngeal cancer (T1), the prognosis with treatment is good and mortality may be favourably compared to that of the normal population matched by age.

2. The following factors adversely affect outcome of treatment by primary radiotherapy:
   a) Pre-malignant conditions - chronic laryngeal nucosa disease
   b) Dosages lower than 6000 rads on the KV 250 machine
   c) Lesions on the left vocal cord show higher tendencies to recur.

3. With meticulous follow up, over 80% of the recurrences following radiotherapy can be salvaged. Recurrences in patients with pre-malignant conditions are best treated by total laryngectomy.

4. In a clinical set up where follow up may be difficult due to socio-economical or manpower reasons, patients with laryngeal carcinoma arising from a chronic laryngeal mucosa disease are recommended for primary surgical therapy.

5. Second primaries (concomitant or otherwise) may occur as much as 13% and these adversely influence the prognosis. A thorough systematic appraisal of these patients is emphasized.

6. The anatomical site of the primary cancer on the glottis does not seem to jeopardize the outcome following radiotherapy in early (T1) glottic carcinoma lesions. Appropriately and accurately staged, these lesions are superficial and in the absence of complicating factors (laryngitis) response to primary curative radiotherapy is good.

7. The low incidence of primary subglottic laryngeal carcinoma with its attending poor prognosis is confirmed.

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APPENDIX 1

Protocol on a retrospective study of laryngeal carcinoma (T1)

1. Personal particulars

Name no: sex: m/f age:

Date of birth

Date of onset

Date of presentation

2. Presenting symptoms duration

Hoarseness .

Dyspnoea .

Dysphagia .

Pain .

3. Signs

Localised lesion T [ ]

Nodal metastases N [ ]

Distant metastases M [ ]
site(s)

4. Tumour stage in 1973

T	
N	
M	

5. Localisation (endoscopic)

1. Right/Left

2. Supraglottic
   - false cord .
   - epiglottic .
   - aryepiglottic .
   - arytenoid .

3. Epilarynx

4. Glottic
   - vocal cord — anterior/middle/posterior.
   - anterior commissure .
   - extension — supraglottic .
     infraglottic .
   - vocal cord motility
     - diminished .
     - fixed .
     - normal .

4. Subglottic .

6. Histological diagnosis

1. Squamous cell carcinoma .
   - well differentiated .
   - moderately well differentiated .
   - poorly differentiated .
2. Anaplastic carcinoma .
3. Others

7. Therapy

1. X-ray

Supervoltage .

Orthovoltage .

Dose (rads) .

Fractionation .

Duration .

Complications noted:

1.

2.

3.

4.

5.

2. Surgery

Indication

Duration following diagnosis

Procedure

total laryngectomy
partial laryngectomy
neck dissection
hemithyroidectomy

others

Any complications?

3. Combined surgery/radiotherapy

Why?
a. failed surgery .

b. failed radiotherapy .

c. adjunct radiotherapy .

d. dosage (rads) .

8. Outcome of therapy (follow up)

Status	Duration in years							
	1	2	3	4	5	6	7	8
no evident disease								
alive with disease								
died of disease								
* died of other causes								
lost to follow up								

* If died of other cause, state the cause

Note: Use the letter as follows:

a = 3 months
b = 6 months
c = 9 months
d = 12 months

with the year as applicable

This applies also to 9 and 10 below.

9. Recurrent disease

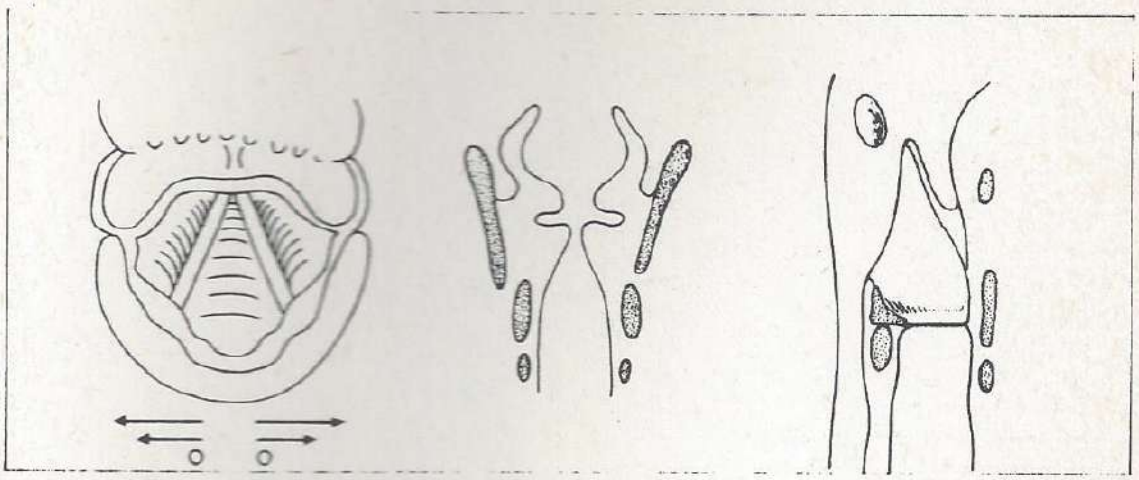
Status	Duration following therapy							
	1	2	3	4	5	6	7	8
Local recurrence								
Regional recurrence								
* Distant metastases								

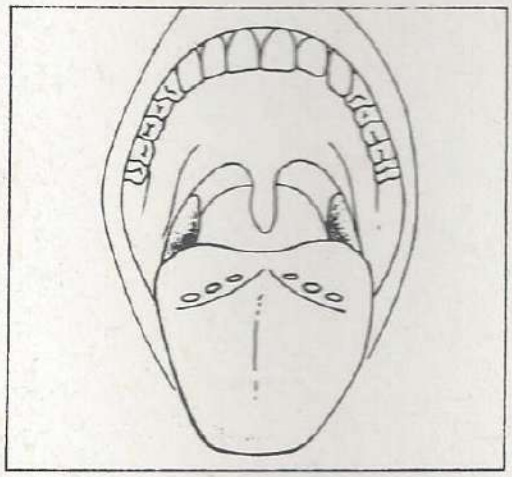
* If distant metastases indicate site

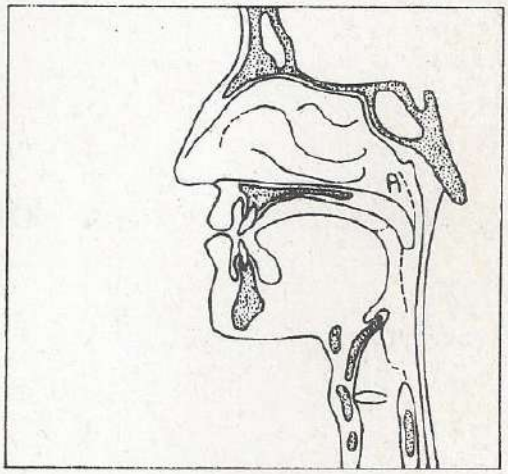
10. Therapy for the recurrences

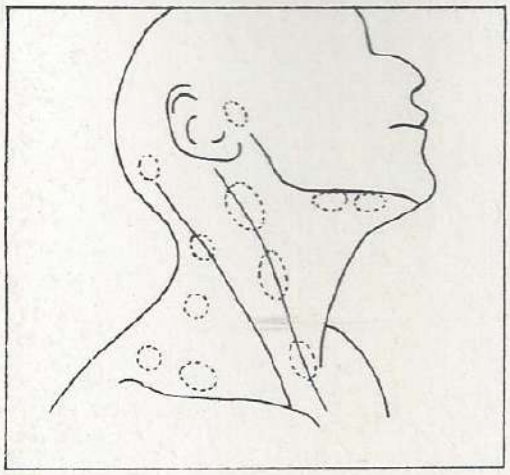
Type	Duration following primary therapy							
	1	2	3	4	5	6	7	8
X-ray								
Surgery								
Chemotherapy								

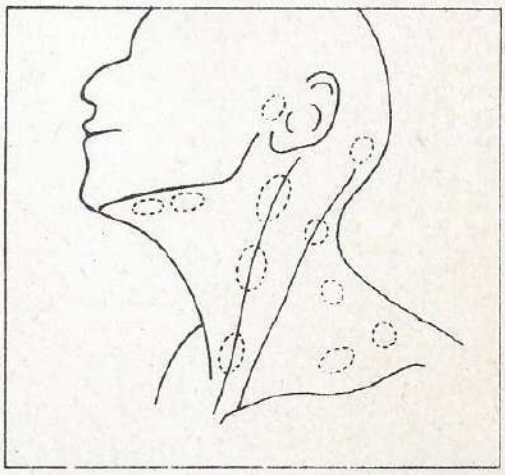
11. Any other data (as the need may arise)











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APPENDIX 2

Berkson-Gage form (1958) for presenting end results *)

Table no.: 1 Title: GLOTTIC CARCINOME CASES. Trial: Date:

interval no.	column 1 interval years after admission	column 2 alive at beginning of interval	column 3 died of cancer during interval	column 4 died of other causes during interval	column 5 lost to follow-up study during interval	column 6 withdrawn alive during interval	column 7 effective number exposed to risk	column 8 percentage dying	column 9 percentage surviving	column 10 cumulative percentage of survivors	column 11 effective sample size
1	0-2	177	1	4	2	21	165.5	3.0	97.0	97.0	165.5
2	1-2	149	4	1	0	21	138.5	3.6	96.4	93.5	152.1
3	2-3	123	1	1	1	14	115.5	1.7	98.3	91.9	145.0
4	3-4	106	3	4	0	19	96.5	7.3	92.7	85.2	122.2
5	4-5	80	0	2	2	11	73.5	2.7	97.3	82.9	114.6
6	5-6	65	0	4	0	13	58.5	6.8	93.2	77.2	96.6
7	6-7	48	0	1	3	7	43.0	2.3	97.7	75.4	90.3
8	7-8	37	0	0	0	7	33.5	0.0	100.0	75.4	90.3
9	8-9	30	0	1	0	6	27.0	3.7	96.3	72.6	74.9
10	9-10	23	0	0	0	4	21.0	0.0	100.0	72.6	74.9
notes:	>10-15	19	0	2	0	15	11.5	17.4	82.6	60.0	28.6

*) W.S.MacComb: Reporting End Results, American Journal of Surgery, 114 (1967) 486-488

Berkson-Gage form (1958) for presenting end results *)

Table no.: 2 Title: SUPRAGLOTTIC CARCINOMA CASES. Trial: Date:

interval no.	column 1 interval years after admission	column 2 alive at beginning of interval	column 3 died of cancer during interval	column 4 died of other causes during interval	column 5 lost to follow-up study during interval	column 6 with-drawn alive during interval	column 7 effective number exposed to risk	column 8 per-centage dying	column 9 per-centage surviving	column 10 cumula-tive per-centage of survivors	column 11 effective sample size
1	0-1	38	1	3	2	5	34.5	11.6	88.4	88.4	34.5
2	1-2	27	0	0	0	5	24.5	0	100.0	88.4	34.5
3	2-3	22	0	0	1	10	16.5	0	100.0	88.4	34.5
4	3-4	11	0	0	0	1	10.5	0	100.0	88.4	34.5
5	4-5	10	0	1	0	0	10.0	10	90.0	79.6	17.2
6	5-6	9	0	0	1	4	6.5	0	100.0	79.6	17.2
7	6-7	4	0	0	0	1	3.5	0	100.0	79.6	17.2
8	7-8	3	0	0	0	0	3.0	0	100.0	79.6	17.2
9	8-9	3	0	0	0	0	3.0	0	100.0	79.6	17.2
10	9-10	3	0	0	0	0	3.0	0	100.0	79.6	17.2
notes:	>10-15	3	0	0	0	0	3.0	0	100.0	79.6	17.2

*) W.S.MacComb: Reporting End Results, American Journal of Surgery, 114 (1967) 486-488.

Berkson-Gage form (1958) for presenting end results *)

Table no.: 3 Title: GLOTTIC CARCINOMA CASES (WITHOUT CHRONIC LARYNGITIS. ◇) Trial: Date:

	column 1	column 2	column 3	column 4	column 5	column 6	column 7	column 8	column 9	column 10	column 11
interval no.	interval years after admission	alive at beginning of interval	died of cancer during interval	died of other causes during interval	lost to follow-up study during interval	with-drawn alive during interval	effective number exposed to risk	per-centage dying	per-centage surviving	cumula-tive per-centage of survivors	effective sample size
1	0-1	130	1	2	2	16	121.0	2.5	97.5	97.5	121.0
2	1-2	109	3	0	0	15	101.5	3.0	94.6	94.6	111.0
3	2-3	91	1	1	1	10	85.5	2.3	92.4	92.4	103.7
4	3-4	78	2	4	0	14	71.0	8.5	84.5	84.6	87.0
5	4-5	58	0	1	2	5	54.5	1.8	83.1	83.1	83.8
6	5-6	50	0	2	0	11	44.5	4.5	79.3	79.3	74.6
7	6-7	37	0	1	3	7	32.0	3.1	76.8	76.8	67.0
8	7-8	26	0	0	0	4	24.0	0	76.8	76.8	67.0
9	8-9	22	0	1	0	3	20.5	4.9	73.1	73.1	52.6
10	9-10	18	0	0	0	2	17.0	0.0	73.1	73.1	52.6
notes:	>10-15	16	0	2	0	12	10.0	20.0	58.5	58.5	22.2

*) W.S.MacComb: Reporting End Results, American Journal of Surgery, 114 (1967) 486-488.

Berkson-Gage form (1958) for presenting end results *)

Table no.: 4 Title: GLOTTIC CARCINOMA (WITH CHRONIC LARYNGITIS) ◆ Trial: Date:

	column 1	column 2	column 3	column 4	column 5	column 6	column 7	column 8	column 9	column 10	column 11
interval no.	interval years after admission	alive at beginning of interval	died of cancer during interval	died of other causes during interval	lost to follow-up study during interval	with-drawn alive during interval	effective number exposed to risk	per-centage dying	per-centage surviving of	cumula-tive per-centage survivors	effective sample size
1	0-1	48	0	2	0	5	45.5	4.4	95.6	95.6	45.5
2	1-2	41	1	1	0	6	38.0	5.3	94.7	90.6	42.1
3	2-3	33	0	0	0	4	31.0	0.0	100.0	90.6	42.1
4	3-4	29	1	0	0	5	26.5	3.8	96.2	87.2	37.3
5	4-5	23	0	1	0	6	20.0	5.0	95.0	82.8	31.6
6	5-6	16	0	2	0	2	15.0	13.3	86.7	71.8	23.4
7	6-7	12	0	0	0	0	12.0	0.0	100.0	71.8	23.4
8	7-8	12	0	0	0	3	10.5	0.0	100.0	71.8	23.4
9	8-9	9	0	0	0	3	7.5	0.0	100.0	71.8	23.4
10	9-10	6	0	0	0	2	5.0	0.0	100.0	71.8	23.4
notes:	10-15	4	0	0	0	3	2.5	0.0	100.0	71.8	23.4

*) W.S.MacComb: Reporting End Results, American Journal of Surgery, 114 (1967) 486-488.

Berkson-Gage form (1958) for presenting end results *)

Table no.: 5 Title: GLOTTIC CARCINOMA (DEAD OF DISEASE + CHRONIC LARYNGITIS) Trial: Date:

	column 1	column 2	column 3	column 4	column 5	column 6	column 7	column 8	column 9	column 10	column 11
interval no.	interval years after admission	alive at beginning of interval	died of cancer during interval	died of other causes during interval	lost to follow-up study during interval	with-drawn alive during interval	effective number exposed to risk	per-centage dying	per-centage surviving	cumula-tive per-centage of survivors	effective sample size
1	0-1	42	0		-0	5	39.5	0.0	100.0	39.7	39.5
2	1-2	37	1		0	6	34.0	2.9	97.1	33.0	34.0
3	2-3	30	0		0	4	28.0	0.0	97.1	28.0	34.0
4	3-4	26	1		0	5	23.5	4.3	100.0	22.5	27.3
5	4-5	20	0		0	6	17.0	0.0	95.7	17.0	27.3
6	5-6	14	0		0	2	13.0	0.0	100.0	13.0	27.3
7	6-7	12	0		0	0	12.0	0.0	100.0	13.0	27.3
8	7-8	12	0		0	3	12.0	0.0	100.0	13.0	27.3
9	8-9	9	0		0	3	12.0	0.0	100.0	13.0	27.3
10	9-10	6	0		0	2	12.0	0.0	100.0	13.0	27.3
notes:	>10-15	4	0		0	3	12.0	0.0	100.0	13.0	27.3

*) W.S.MacComb: Reporting End Results, American Journal of Surgery, 114 (1967) 486-488.

Berkson-Gage form (1958) for presenting end results ¤)

Table no.: 6 Title: ACC GLOTTIC CARCINOMA CASES WITH OR WITHOUT CHRONIC LARYNGITIS. Trial: Date:

	column 1	column 2	column 3	column 4	column 5	column 6	column 7	column 8	column 9	column 10	column 11
interval no.	interval years after admission	alive at beginning of interval	died of cancer during interval	died of other causes during interval	lost to follow-up study during interval	with-drawn alive during interval	effective number exposed to risk	per-centage dying	per-centage surviving	cumula-tive per-centage of survivors	effective sample size
1	0-1	158	1	0	0	23	146.5	0.7	99.3	99.3	146.5
2	1-2	134	4	0	0	21	123.5	3.2	96.8	96.1	127.6
3	2-3	109	1	0	0	15	101.5	1.0	99.0	95.2	122.4
4	3-4	93	3	0	0	19	83.5	3.6	96.4	91.7	104.5
5	4-5	71	0	0	0	13	64.5	0.0	100.0	91.7	104.5
6	5-6	58	0	0	0	13					
7	6-7	45	0	0	0	10					
8	7-8	35	0	0	0	7					
9	8-9	28	0	0	0	6					
10	9-10	22	0	0	0	4					
notes	10-15	18	0	0	0	15					

¤) W.S.MacComb: Reporting End Results, American Journal of Surgery, 114 (1967) 486-488.

Berkson-Gage form (1958) for presenting end results *)

Table no.: 7 Title: DEAD OF DISEASE; GLOTTIC CARCINOMA CASES WITHOUT CHRONIC LARYNGITIS. △ Trial: Date:

	column 1	column 2	column 3	column 4	column 5	column 6	column 7	column 8	column 9	column 10	column 11
interval no.	interval years after admission	alive at beginning of interval	died of cancer during interval	died of other causes during interval	lost to follow-up study during interval	withdrawn alive during interval	effective number exposed to risk	percentage dying	percentage surviving	cumulative percentage of survivors	effective sample size
1	0-1	116	1	-	2	16	107.0	0.9	99.1	99.1	107.0
2	1-2	97	3	-	0	15	89.5	3.4	96.6	95.7	93.4
3	2-3	79	1	-	1	10	73.5	1.4	98.6	94.4	88.7
4	3-4	67	2	-	0	14	60.0	3.3	96.7	91.3	77.0
5	4-5	51	0	-	2	5	47.5	0.0	100.0	91.3	77.0
6	5-6	44	0	-	0	11		0.0	100.0	91.3	77.0
7	6-7	33	0	-	3	7		0.0	100.0	91.3	77.0
8	7-8	23	0	-	0	4		0.0	100.0	91.3	77.0
9	8-9	19	0	-	0	3		0.0	100.0	91.3	77.0
10	9-10	16	0	-	0	2		0.0	100.0	91.3	77.0
notes:	10-15	14	0	-	0	12		0.0	100.0	91.3	77.0

*) W.S.MacComb: Reporting End Results, American Journal of Surgery, 114 (1967) 486-488.

Berkson-Gage form (1958) for presenting end results *)

Table no.: 8 Title: DOOC / GLOTTIC CARCINOMA WITH CHRONIC LARYNGITIS. Trial: Date:

	column 1	column 2	column 3	column 4	column 5	column 6	column 7	column 8	column 9	column 10	column 11
interval no.	interval years after admission	alive at beginning of interval	died of cancer during interval	died of other causes during interval	lost to follow-up study during interval	with-drawn alive during interval	effective number exposed to risk	per-centage dying	per-centage surviving	cumula-tive per-centage of survivors	effective sample size
1	0-1	46		2	0	5	43.5	4.6	95.4	95.4	43.5
2	1-2	39		1	0	6	36.0	2.8	97.2	92.8	41.1
3	2-3	32		0	0	4	30.0	0	100.0	92.8	41.1
4	3-4	28		0	0	5	25.5	0	100.0	92.8	41.4
5	4-5	23		1	0	6	20.0	5.0	95.0	88.1	29.8
6	5-6	16		2	0	2	15.0	13.3	86.7	76.4	20.9
7	6-7	12		0	0	0		0.0	100.0	76.4	20.9
8	7-8	12		0	0	3		0.0	100.0	76.4	20.9
9	8-9	9		0	0	3		0.0	100.0	76.4	20.9
10	9-10	6		0	0	2		0.0	100.0	76.4	20.9
notes:	10-15	4		0	0	3		0.0	100.0	76.4	20.9

*) W.S.MacComb: Reporting End Results, American Journal of Surgery, 114 (1967) 486-488.

Berkson-Gage form (1958) for presenting end results *)

Table no.: 9 Title: DOOC / GLOTTIC CARCINOMA WITHOUT CHRONIC LARYNGITIS Trial: Date:

	column 1	column 2	column 3	column 4	column 5	column 6	column 7	column 8	column 9	column 10	column 11
interval no.	interval years after admission	alive at beginning of interval	died of cancer during interval	died of other causes during interval	lost to follow-up study during interval	withdrawn alive during interval	effective number exposed to risk	percentage dying	percentage surviving	cumulative percentage of survivors	effective sample size
1	0-1	123		2	2	16	114.0	1.8	98.2	98.2	114.0
2	1-2	103		0	0	15	95.5	0	100.0	98.2	114.0
3	2-3	88		1	1	10	82.5	1.2	98.2	97.1	99.4
4	3-4	76		4	0	14	69.0	5.8	94.2	91.4	78.3
5	4-5	58		1	2	5	54.5	1.8	98.2	89.8	74.1
6	5-6	50		2	0	11	44.5	4.5	95.5	85.7	64.1
7	6-7	37		1	3	7	32.0	3.1	96.9	83.0	56.6
8	7-8	26		0	0	4	24.0	0.0	100.0	83.0	56.6
9	8-9	22		1	0	3	20.5	4.9	95.1	79.0	43.6
10	9-10	18		0	0	2	17,0	0	100.0	79.0	43.6
notes:	10-15	16		2	0	12	10.0	20.0	80.0	63.2	18.7

*) W.S.MacComb: Reporting End Results, American Journal of Surgery, 114 (1967) 486-488.

Berkson-Gage form (1958) for presenting end results *)

Table no.: 10 Title: GLOTTIC CARCINOMA RECURRENCES DOD + DOOC Trial: Date:

	column 1	column 2	column 3	column 4	column 5	column 6	column 7	column 8	column 9	column 10	column 11
interval no.	interval years after admission	alive at beginning of interval	died of cancer during interval	died of other causes during interval	lost to follow-up study during interval	with-drawn alive during interval	effective number exposed to risk	per-centage dying	per-centage surviving	cumula-tive per-centage of survivors	effective sample size
1	0-1	32	1	-		0	32.0	3.1	96.9	96.9	32.0
2	1-2	31	2	1		1	30.5	9.8	90.2	87.3	31.6
3	2-3	27	0	1		2	26.0	3.8	96.2	84.0	31.1
4	3-4	24	2	-		5	21.5	9.3	90.7	76.2	28.7
5	4-5	17	1	-		5	14.5	6.9	93.1	70.9	25.6
6	5-6	11	0	-		1	10.5	0.0	100.0	70.9	25.6
7	6-7	10	0	-		1	9.5	0.0	100.0	70.9	25.6
8	7-8	9	0	-		0	9.0	0.0	100.0	70.9	25.6
9	8-9	9	0	-		0	9.0	0.0	100.0	70.9	25.6
10	9-10	9	0	-		1	8.5	0.0	100.0	70.9	25.6
11	10-15	8	0	1		5	5.5	18.2	81.8	58.0	12.8
12	15	2	0	-		-	-				

*) W.S.MacComb: Reporting End Results, American Journal of Surgery, 114 (1967) 486-488.