a clinical review on dose response in radiotherapy for laryngeal carcinoma

a.b.m.f. karim

A CLINICAL REVIEW ON DOSE RESPONSE

IN RADIOTHERAPY FOR LARYNGEAL CARCINOMA

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VRIJE UNIVERSITEIT TE AMSTERDAM

A CLINICAL REVIEW

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door

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geboren te Bangladesh

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To

Nihar, Refaat and Andromeda

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PREFACE AND OBJECTIVES

PREFACE AND OBJECTIVES

Preface

The radiotherapist used to treat patients with carcinoma with the maximum tolerated fractionated dose during the orthovoltage era. Higher dosage has been practised with the same quality of radiation with increased fractionation and time, particularly when a smaller volume of tissue was the target of interest. The same basic pattern can be seen in the era of supervoltage radiations, but the desire to deliver higher dosage becomes fulfilled.

The experimentations have culminated in an empirical and successful pattern of radiation treatment of carcinoma of the larynx and efforts have been made to compare the different dosage schedules with a view to find out the optimum, with maximum control of tumors with minimum complications.

Radiotherapy, in contrast to other clinical disciplines, perhaps uses in day-to-day practice, a more physically oriented and mathematically defined dose system. Yet, owing to individual biological variability of the tumor and the normal tissue responses, dosimetric characteristics, different points of view of the individual radiotherapist and many other factors, the correlation between the precise dose delivered and the effect, in relation to the local control of the cancer and the complications, remains obscure.

So, **dose-response**, indicating higher rates of local control with increasing dose, may be one important aspect to analyse and study.

The search for the optimum is easier in the presence of dose response of a tumor.

Mathematical approaches that may be applied to evaluate an optimal dose system with maximum cure-rate and minimum complication-rate are being sought by Rubin et al (1972) and Mendelsohn (1972); but importance to their ideas is not stressed in day-to-day clinical radiotherapy.

Over the years many studies have been published on the radiation treatment of carcinoma of the larynx. In general, the high success rate for early tumors is evident in these publications.

However, controversies exist in the field of planned primary radiation treatment methods. Similarly, treatment schemes and policies vary in different centres. In some centres, laryngectomies are routinely performed more frequently, either primarily or with pre- or post-operative radiotherapy. A few controlled studies shall be needed to solve the controversies. Meanwhile, the individual centres must continue to study their clinical material to collect enough data about tumor responses, cure and complication rates to provide detailed fundamental knowledge which, in general, is lacking (Morrison 1975) in the field of radiation treatment.

Cancer of the larynx is one of the rewarding diseases to treat by radiotherapy. Many publications have utilized the Nominal Standard Dose (N.S.D.) concept of Ellis (1967, 1968) to compare the different treatment schemes in an attempt to assess the optimum dose. Basically the N.S.D. concept is helpful to compare the different treatment regimes in a mathematical model. The concept considers relations of dose, time and fractionation of a treatment method when the dose of radiation used is up to the level of maximum tolerance particularly in relation to the mesenchymal connective tissue. "The N.S.D. represents a cell killing effect and that depends on absorbed dose" following Ellis (1975P).

The Nominal Standard Dose is expressed in unit of ret indicating Rad Equivalent Therapy and is obtained by the mathematical expression:

$$\text{N.S.D. in rets} = \text{Total tumor dose (TD)} \times \text{No. of fractions (N)}^{-0.24} \times \text{No. of days (T)}^{-0.11}$$

Kirk et al (1971, 1975, 1976) and Eads (1972) have attempted to modify the concept, in particular to incorporate volume as was thought by Cohen (1962).
So far however, neither modifications has been frequently utilized. It is of course well-known that the volume of the disease or the target areas has an important role to play (Strandquvist 1944, Shukovsky 1970, Moss et al 1973, Fletcher et al 1974, Ellis 1975P, 1976P).
Greater tumor mass needs a higher radiation dose for eradication of the solid cancers. Yet higher dose is more difficult to deliver and is scarcely practised when the volume of the tumor is greater. The same dose in the same time to a larger volume or target invites unacceptable incidence of complications. The higher rate of complications will depend on the different types of tissues encompassed in the target volume. In advanced laryngeal carcinoma, one has to consider the spinal cord, cartilage, thyroid gland etc. and their different tolerance doses. This means that a technique may have to be evolved to avoid the most vulnerable structure e.g. the spinal cord should be avoided at least after a certain dose level. Other tissues, if likely to be involved, must remain within the treatment field and the volume factor may have to be managed by decreasing the daily dose and increasing the time and the number of fractionations. This approach in some situations at least appears to be practical, yet rarely practised.
By bringing the volume factor into the mathematical concept of N.S.D. one may introduce other complex factors and assessment of optimal dose range may be more difficult. The problem of incorporating volume in any treatment schedule is well-focussed by Ellis (1976P) himself:
"As regards the use of the N.S.D. concept I differ from Eads in that I believe that an allowance should not be made for area or volume

except by increasing the time. It seems to me for instance, that if one has a larger tumor to treat, since there are more cells the dose given should be larger and not smaller and if the volume is so large that a certain schedule will produce too much late effect, than keeping to the same NSD which represents normal tissue tolerance related to cell survival then it may be necessary to increase the time so as to be able to reach the NSD concerned. On the other hand, in the case of certain organs I'm sure the volume is important but not as a matter of cubic centimeters but rather as a proportion of the organ. For instance, it is possible to irradiate a third of the kidney without destroying the kidney function. If one treats arytenoid cartilage in its entirety, although it requires only a small field to do so, if the dose has been big enough to destroy the perichondrium, the cartilage will necrose and there will be a complication problem in the larynx. In the case of the bowel the length of the bowel which is treated to a high dose and might therefore become stiff and inelastic is important and it is probably the proportion of bowel so affected that matters more than the actual volume in cubic centimeters".
One is aware of the multitude of the critical comments on the concept by Liversage (1971), Berry et al (1974), Fowler (1971), Kok (1971), Loeffler (1974), Fletcher et al (1974) and many others.
Nevertheless, the N.S.D. concept is gaining popularity rapidly. Whereas only 7 papers in the international journals utilized the N.S.D. concept in 1969 and 1970, the number rose to 17 in 1973 and to 22 in 1974 (Orton 1975). By now almost all papers on radiotherapy utilize the N.S.D. concept to obtain a norm.
Without the N.S.D. as yardstick, it would be impossible to compare the different dose systems as normalization will not be possible.
Kirk (1971), who has a number of studies on the Cumulative Radiation Effect (C.R.E.) himself admits (1976), "The numerical values (of C.R.E.) are the same as N.S.D. rets". So far, no clinical material has come out with Ead's (1972) modifications of the N.S.D. concept. More recently Wara (1975) and Wollin et al (1976) have published on the concept of Equivalent Dose (ED) and Biologic Index of Reactions (B.I.R.) respectively but wider clinical experience is not so far published. Orton and Ellis published in 1973 on TDF (Tumor, Dose and Fractionations) factors to simplify the use of the N.S.D. concept in practical radiotherapy. Kok (1971, 1977P) has perhaps studied the problem most extensively from the point of view of radiation tolerance of laryngeal tissues and concludes (1977P) in favour of using the N.S.D. as a yardstick.
On these considerations, the N.S.D. concept of Ellis has been accepted in this study to get norms for differing dose schedules.
When analysing the results of radiation treatment, one must place proper importance on studying the benefit of cure. The most important one is the control of the primary tumor. The primary tumor is conven-

tionally studied by regions, extent, histological grading, other biological parameters in relation to the local control or the survival of a group of patients but less frequently by dose-response considerations. All studies should analyse the quality of voice, as this is a crucial point in favour of radiotherapy. The incidence of major complications, the failures, the control of failures by salvage surgery should be studied as points of major importance. Controversies on the optimum treatment policy are well-known but nonetheless one should aim at improvement of the results of control of the primary tumor of the larynx. While these factors are analysed, the local control of the tumor should be reviewed with the help of the available mathematical model in an attempt to assess the optimum dose range which is supposed to be within a small critical range (Moss et al 1973). The following considerations therefore, form the basis of this study:

Objectives of the study

All surviving patients consecutively treated for larynx-carcinoma by radiotherapy for a decade (1965-1974) in the Academic Hospital of the Free University (AZVU) in Amsterdam have been followed up personally with a checklist protocol with the following objectives:

1. To obtain dose response data for the patients with carcinoma of the larynx in each stage category. The N.S.D. concept of Ellis in day-to-day practice is applied in the form of ret dose. Local control of the tumor with a minimum follow-up period of 2 years has been accepted as response in relation to the dose delivered. Major complications if less than 5% have been considered as acceptable.

2. To attempt to solve some of the controversies that are found in the literature on the treatment of each subgroup of carcinoma of the larynx, particularly on the dose-dependence of glottic carcinomas.

3. To define optimum dose range for laryngeal carcinomas.

   To fulfil such objectives in an efficient and accurate manner, electronic data handling systems are usually preferred. So, it is attempted to develop and assess the feasibility of the use of checklists, protocols and computer data based programmes in day-to-day data storage, retrieval and clinical research in radiation oncology.

The records of the patients with carcinoma of the larynx, who died during the period 1965-1974, are analysed in a retrospective way to obtain similar information to be fed to the computerized data retrieval system, so developed.

PART I

REVIEW OF THE LITERATURE

1 INTRODUCTION AND TNM CLASSIFICATIONS

Laryngeal carcinoma has been aptly called "A testing ground for the radiotherapist" by Lederman (1971). Within a few years of the discovery of X-rays, the pioneers like Voigt (1896), Scheppegrell (1902), Delevan (1902), etc. started treating head and neck cancers.
Special X-ray tubes were being manufactured for the treatment of cancer of the larynx. The progress in the field however became severely limited by complications.
In the Netherlands, the important contributions of Daniel den Hoed (1948), one of the pioneers in developing "Intra-cavitary röntgentherapy of malignant tumors" of the larynx, will always be remembered. The other important Dutch studies are from Stam (1953), Struben (1961), Landman (1966), Gerlings (1970), Snow (1970), Kok (1971), de Jong (1975), Kazem (1975) and v.d. Broek (1977). While detailed diagnostic and therapeutic aspects are excellently described by Stam, Struben and Landman, Gerling covers the important question of new primaries in patients cured from laryngeal carcinoma. Snow deals with the problems of metastasis. De Jong primarily concerns himself with surgical treatment whereas Kazem and v.d. Broek detail aspects of planned combined treatment by radiotherapy and surgery. Hordijk (1977) has published on treatment of laryngeal carcinoma with particular emphasis on sandwich treatment, surgery being sandwiched between pre- and post operative radiotherapy. Kok persistently evaluates radiotherapeutic late complication in the light of available mathematical models to get norm for differing dose schedules used for laryngeal carcinoma.
Historically, the French workers led by Coutard (1922) and the British led by Finzi (1928) may well claim to have the greatest experience in treating the disease by radiations, both external and interstitial, in the early pioneering days.
The first comprehensive publication in English on external radiotherapy of laryngeal cancer is from Henri Coutard (1932). It is fascinating to note that Coutard touched almost every important point e.g. local control rate at 2 years, survival rates up to 9 years, combined surgical and radiotherapeutic approach, dose time fractionation, volume considerations, sequelae, repair processes and steps to reduce cartilage necrosis. The other paper with significant contribution is from Finzi (1928), the father of the well-known Finzi-Harmer technique for treating carcinoma of the larynx by brachytherapy. He placed great importance on the quality of voice and this is revealed by, "Lantern slide diagrams of the condition of the vocal cords before and after the treatment were shown. Gramophone records, which had been specially made free of cost by the kindness of the Columbia Gramophone Company were used to illustrate the voice results and for comparison the records of two cases treated by the operation of laryngofissure were included".

Since then a number of publications have appeared and each one has its say. These publications are reviewed keeping in mind an up-to-date staging system such as TNM. Unfortunately, the TNM classification has been changed over the years. However, in view of the changing staging systems, many facets may be studied from the vast literature that exists on laryngeal carcinoma. The relevant aspects for this study to be reviewed from the literature are thought to be:

1. Dose response in relation to the different regions specially with reference to the (T) of the TNM classifications.
2. Other prognostic factors.
3. Complications following radiotherapy particularly in relation to the local control of the tumor.
4. Voice in the patients with local control of the tumor by radiotherapy.

All the TNM classifications are recapitulated here for the convenience of reference:

1.1 TNM CLASSIFICATIONS OF THE UNION INTERNATIONALE CONTRE LE CANCER (U.I.C.C.).

LARYNX
Classified 1962. Trail period 1963 - 1972

The classification applies only to carcinoma.
There must be histological verification of the disease.
The extent of disease is assessed on clinical examination, endoscopy and radiography.
The regional lymph nodes are the cervical nodes.
The larynx is divided into three regions and these are sub-divided into a number of sites, thus:

Regions:	Sites:
(a) Supraglottic	Posterior surface of the epiglottis excluding the tip of the epiglottis and the aryepiglottic fold (marginal zone). Arytenoid. Ventricular bands. Ventricular cavities
(b) Glottic	Vocal cords. Anterior commissure. Posterior commissure.
(c) Subglottic	

A stage-grouping is not at present recommended.

T - Primary tumour

(a) Supraglottic

TIS Pre-invasive carcinoma, so-called carcinoma in situ.
T1 Tumour confined to laryngeal surface of epiglottis, or to an aryepiglottic fold or to a ventricular cavity or a ventricular band.
T2 Tumour involving the epiglottis and extending to the ventricular cavities or bands.
T3 Tumour of the epiglottis and/or ventricles or ventricular bands, and extending into the cords.
T4 Tumour as in T1, T2 or T3, but with direct extension to piriform sinus, postcricoid region, vallecula or base of tongue.

(b) Glottic

TIS Pre-invasive carcinoma, so-called carcinoma in situ.
T1 Tumour confined to one vocal cord, mobility of which remains normal.
T2 Tumour involving both cords with normal mobility or one or both cords with fixation of cords.
T3 Tumour extending from cord either to subglottic region or to supraglottic region (i.e. to ventricular bands or ventricles).
T4 Tumour as in T1, T2, or T3, but with direct extension through cartilage to skin, to the piriform sinus or to the postcricoid region.

(c) Subglottic

TIS Pre-invasive carcinoma, so-called carcinoma in situ.
T1 Tumour limited to one side of the subglottic region, exclusive of the under surface of the cord.
T2 Tumour extending to two sides of subglottic region, exclusive of the under surface of the cord.
T3 Tumour involving the subglottic region and extending to the cords.
T4 Tumour as in T1, T2, or T3, but with direct extension to trachea, skin or postcricoid region.

N - Regional lymph nodes

The clinician may record whether palpable nodes are considered to contain growth or not.
NO No palpable nodes.
N1 Movable homolateral nodes.
N1a Nodes not considered to contain growth.
N1b Nodes considered to contain growth.
N2 Movable contralateral or bilateral nodes.
N2a Nodes not considered to contain growth.
N2b Nodes considered to contain growth.
N3 Fixed Nodes.

M - Distant metastases

MO No evidence of distant metastases.
MI Distant metastases present.

1.2 TNM CLASSIFICATION OF THE UNION INTERNATIONALE CONTRE LE CANCER (U.I.C.C.)

LARYNX
Classified 1972. Trial period 1973 - 1977

Introductory notes.

1. Regions. The supraglottic region is divided into two optional sub-regions in order that specialists may record epilaryngeal tumors separately if they so wish.
2. Glottis. In the definition of T2 the term "impaired mobility" is used. This is included to satisfy those laryngologists who consider that a cord may be fully mobile, partially mobile or fixed.
3. Regional nodes. The definitions of the N categories are identical with those for all other Head and Neck sites.

The clinical classification may not be changed but information regarding the assessment of the regional lymph nodes may be added to the N category thus:
N – (minus) for nodes with no microscopic evidence of metastasis; or N + (plus) for nodes with microscopic evidence of metastasis.

Rules for classification

The classification applies only for carcinoma.
There must be histological verification of the disease.
The extent of the disease is assessed on clinical examination, endoscopy and radiography.
The regional lymph nodes are the cervical nodes.
The larynx is divided into three regions and these may be sub-divided into a number of sites, thus:

Regions:		Sites:
1. Supraglottis		
	(i) Epilarynx (including Marginal zone)	Posterior surface of suprahyoid epiglottis (including the tip) Aryepiglottic fold Arytenoid
	(ii) Supraglottis, excluding epilarynx	Infra-hyoid epiglottis Ventricular bands (false cords) Ventricular cavities
2. Glottis		Vocal cords Anterior commissure Posterior commissure
3. Subglottis		

TNM Classification

T - Primary Tumour.

1. Supraglottis

TIS Pre-invasive carcinomas (carcinoma in situ).
T1 Tumour limited to the region with normal mobility.
- T1a Tumour confined to the laryngeal surface of the epiglottis or to an aryepiglottic fold or to a ventricular cavity or to a ventricular band.
- T1b Tumour involving the epiglottis and extending to the ventricular cavities or bands.

T2 Tumour of the epiglottis and/or ventricles or ventricular bands, and extending to the vocal cords, without fixation.
T3 Tumour limited to the larynx with fixation and/or destruction or other evidence of deep invasion.
T4 Tumour with direct extension beyond the larynx, i.e. to the pyriform sinus, or the postcricoid region or the vallecula or the base of the tongue.

2. Glottis

TIS Pre-invasive carcinoma (carcinoma in situ).
T1 Tumour limited to the region with normal mobility.
- T1a Tumour confined to one cord.
- T1b Tumour involving both cords.

T2 Tumour extending to either the subglottic, or the supraglottic regions (i.e. to the ventricular bands or the ventricles), with normal or impaired mobility.
T3 Tumours limited to the larynx with fixation of one or both cords.
T4 Tumour extending beyond the larynx i.e. into cartilage or the pyriform sinus or the postcricoid region or the skin.

3. Subglottis

TIS Pre-invasive carcinoma (carcinoma in situ).
T1 Tumour limited to the region with normal mobility.
- T1a Tumour limited to one side of the subglottic region and not involving the under surface of the cord.
- T1b Tumour extending to both sides of the subglottic region and not involving the under surface of the cords.

T2 Tumour involving the subglottic region and extending to one or both cords.
T3 Tumour limited to the larynx with fixation of one or both cords.
T4 Tumour extending beyond the larynx i.e. to the post-cricoid region or the trachea or the skin.

N - Regional Lymph Nodes

N0 Regional lymph nodes not palpable.
N1 Movable homolateral nodes.
- N1a Nodes not considered to contain growth.
- N1b Nodes considered to contain growth.

N2 Movable contralateral or bilateral nodes.
- N2a Nodes not considered to contain growth.
- N2b Nodes considered to contain growth.

N3 Fixed nodes.

M Distant Metastasis.

M0 No evidence of distant metastases.
M1 Distant metastases present.

Stage - Grouping

Stage I	T1	N0 or N1a or N2a	M0
Stage II	T2	N0 or N1a or N2a	M0
Stage III	T3	N0 or N1a or N2a	
	T4	N0 or N1a or N2a	M0
	any T	N1b or N2b	
Stage IV	any T	with N3	M0
	any T	any N with	M1

1.3. AMERICAN JOINT COMMITTEE (A.J.C.) FOR CANCER STAGING AND END RESULTS REPORTING.

1976: T.N.M. classification

Staging cancer of the larynx

The following anatomic definition of "larynx" allows classification of carcinomas arising in the encompassed mucous membranes but excludes cancers arising on the lateral or posterior pharyngeal wall, pyriform fossa, postcricoid areas, and the vallecula, or base of the tongue.

The anterior limit of the larynx is constituted by the anterior or lingual surface of the prahyoid epiglottis, thyrohyoid menbrane, the anterior commissure, and the anterior wall of the subglottic region, which is composed of the thyroid cartilage, the cricothyroid membrane, and the anterior arch of the cricoid cartilage.

The posterior and lateral limits include the aryepiglottic folds, the arytenoid region, the interarytenoid space, and the posterior surface of the subglottic space represented by the mucous membrane covering the cricoid cartilage.

The superior lateral limits are constituted by the tip and the lateral border of the epiglottis.
The inferior limits are constituted by a plane passing through the inferior edge of the cricoid cartilage.

For the purposes of this clinical-stage classification, the larynx is divided into three regions: supraglottis, glottis, and subglottis. The supraglottis is composed of the epiglottis (both its lingual and laryngeal aspects), aryepiglottic folds, arytenoids, and ventricular bands (false cords). The inferior boundary of the supraglottis is a horizontal plane passing through the apex of the ventricle. The glottis is composed of the true vocal cords, including the anterior and posterior commissures. The upper boundary is the horizontal plane passing through the apex of the ventricle, and the lower boundary is a horizontal plane 1 cm below the apex of the ventricle. The subglottis is the region extending from the lower boundary of the glottis to the lower margin of the cricoid cartilage.

The division of the larynx is summarized in this table:

Regions	Sites
Supraglottis	Ventricular bands (false cords) Arytenoids Epiglottis (both lingual and laryngeal aspects) Suprahyoid epiglottis Infrahyoid epiglottis Aryepiglottic folds
Glottis	True vocal cords including anterior and posterior commissures
Subglottis	Subglottis

Definition of "T" Categories of the Larynx.

Supraglottis

- TIS: Carcinoma in situ
- T1: Tumor confined to site of origin with normal mobility
- T2: Tumor involves adjacent supraglottic site(s) or glottis without fixation
- T3: Tumor limited to larynx with fixation and/or extension to involve postcricoid area, medial wall of pyriform sinus, or pre-epiglottic space
- T4: Massive tumor extending beyond larynx to involve oropharynx, soft tissues of neck, or destruction of thyroid cartilage.

Glottis

- TIS: Carcinoma in situ
- T1: Tumor confined to vocal cord(s) with normal mobility (includes involvement of anterior or posterior commissures)
- T2: Supraglottic and/or subglottic extension of tumor with normal or impaired cord mobility
- T3: Tumor confined to larynx with cord fixation
- T4: Massive tumor with thyroid cartilage destruction and/or extension beyond confines of larynx.

Subglottis

- TIS: Carcinoma in situ
- T1: Tumor confined to the subglottic region
- T2: Tumor extension to vocal cords with normal or impaired cord mobility
- T3: Tumor confined to larynx with cord fixation
- T4: Massive tumor with cartilage destruction or extension beyond confines of larynx or both

Cervical Node Classification.

The following regional node classification is applicable to all malignant head and neck tumors. In clinical evaluation the actual size of the nodal mass should be measured and allowance made for intervening soft tissues. It is recognized that most masses over 3 cm in diameter are not single nodes but confluent nodes or tumor in soft tissues of the neck. There are three stages of clinically positive nodes: N1, N2, and N3. The use of subgroups a, b, and c is not required but is recommended. Midline nodes are considered as homolateral nodes.

- NO: No clinically positive node
- N1: Single clinically positive homolateral node less than 3 cm in diameter
- N2: Single clinically positive homolateral node 3 cm to 6 cm in diameter or multiple clinically positive homolateral nodes, none over 6 cm in diameter
  - N2a: Single clinically positive homolateral node 3 cm to 6 cm in diameter
  - N2b: Multiple clinically positive homolateral nodes, none over 6 cm in diameter
- N3: Massive homolateral node(s), bilateral nodes, or contralateral node(s)
  - N3a: Clinically positive homolateral node(s), one over 6 cm in diameter
  - N3b: Bilateral clinically positive nodes (in this situation each side of the neck should be staged separately; that is, N3b–right N2a, left N1)
  - N3c: Contralateral clinically positive node(s) only.

Summary of Stage Groupings

Stage I:	T1, NO, MO	Stage III:	T3, NO, MO
Stage II:	T2, NO, MO		T1 or T2 or T3, N1, MO
		Stage IV:	T4, NO, MO
			any T, N2, MO
			any T, any N, M1.

1.4 Comments on the TNM classifications.

The baseline parameters such as TNM have definitely improved our understanding of the malignant tumors but we have by no means reached an ideal situation. The confusion that existed in the field of laryngeal carcinoma before the 1972 TNM classification is well-described (Table I) by Vermund (1970). Certain weaknesses of the 1972 classification are focussed amongst others by Olofsson et al (1974, 1975), Wang (1974), de Jong (1975) and Karim et al (1976).

The preliminary A.J.C. classification (1976) is most recent and is yet to be practised. Therefore in this study, the 1972 U.I.C.C. classification has been used as this is perhaps up till now the most universally accepted TNM staging system.

Basically the 1962 classification was modified in 1972 by U.I.C.C. on the important pathophysiologic consideration of movement of the vocal cord over and above the question of regional extensions. Thus a glottic tumor with bilateral extension and normally mobile or fixed cord(s) was designated as T2 tumor in 1962 but is re-named as T1b if with normal mobility or T3 if with fixed cord in 1972 U.I.C.C. classification. A small tumor of one region with slight impairment of movement is T2 but with complete fixation is redesignated (1972) as T3 tumor, while previously (1962-1972) they were known as T2 tumor. A small or a large tumor extending to 2 or 3 regions was T3 in 1962 classification but becomes T2 in 1972 if movement is not totally restricted. Importance of movement is stressed amongst others by Lederman (1965, 1970, 1971) and Wang (1974).

The latest (1976) A.J.C. classification incorporates better definition on the anatomy of the regions and deviates from the U.I.C.C. classification on nodal metastasis, as indicated by Fletcher et al (1970).

It corrects some 'grammatical' aspects of the 1972 classification (Karim et al 1976). It also tends to indicate the importance of the tumor mass as stressed by Karim et al (1977) and the term 'massive' is used for all T4 tumors. Certainly, the tumor mass is important in radiotherapy and in future this may be more stressed. The pathophysiological aspect of movement of the cord is however not to be underemphasized.

Table 1

Staging in cancer of the larynx (historical perspective)

Stage	UICC	AJC	Nielsen	Lederman	Taskinen & Holsti	Garland	Bryce et al
I	$T_1N_0M_0$	$T_1N_0M_0$	$T_1N_0M_0$	$T_1N_0M_0$	$T_1N_0M_0$	$T_1N_0M_0$	$T_1N_0M_0$
II	$T_2N_0M_0$	$T_{2-4}N_0M_0$	$T_2N_0M_0$	$T_2T_3N_0M_0$	$T_2N_0M_0$	$T_{2-3}N_0M_0$	$T_2N_0M_0$
	$T_1N_1M_0$				$T_1N_1M_0$		$T_1N_1M_0$
III	$T_{3-4}N_0M_0$	$T_{1-3}N_1M_0$	$T_2T_3N_0M_0$	$T_{2-4}N_0M_0$	$T_3N_0M_0$	$T_{1-3}N_1M_0$	$T_3N_0M_0$
	$T_{2-4}N_1M_0$			$T_1T_4N_1M_0$	$T_{2-3}N_1M_0$		$T_{2-3}N_1M_0$
	$T_{1-4}N_2M_0$				$T_{1-3}N_2M_0$		$T_{1-3}N_2M_0$
IV	$T_{1-4}N_3M_0$	$T_4N_1M_0$	$T_4N_0M_0$	$T_{1-4}N_{2-3}M_0$	$T_4N_{0-2}M_0$	$T_{1-4}N_2M_0$	$T_4N_0M_0$
	$T_{1-4}N_{0-3}M_1$	$T_{1-4}N_2M_0$	$T_{1-4}N_{1-3}M_0$	$T_{1-4}N_{0-3}M_1$	$T_{1-4}N_3M_0$	$T_{1-4}N_{0-3}M_1$	$T_{1-4}N_3M_0$
		$T_{1-4}N_{1-2}M_1$	$T_{1-4}N_{0-3}M_1$		$T_{1-4}N_{0-3}M_1$		$T_{1-4}N_{0-3}M_1$

From Vermund (1970) with his kind permission: Cancer 25, 485. Nielson excluded cases with fixed cord from stage II to place them in stage III.
Lederman placed tumors with impaired mobility in stage II but all fixed cords were in stage III.

The 1972 U.I.C.C. classification is to be tried till 1977 and a modified new classification may soon follow. Perhaps the 'grammatical' errors (Karim et al 1976) will be corrected e.g. a transglottic tumor without complete fixity cannot be classified according to the 1972 U.I.C.C. classification and a supraglottic tumor involving 3 regions without fixity of the vocal cord cannot be classified by either the U.I.C.C. (1972) or the A.J.C. (1976) classification. The TIS brings in added difficulty as advanced growths with concomitant pre-invasive lesions are being reported by some workers as TIS carcinoma e.g. 'carcinoma-in-situ with fixed cord'. Pre-invasiveness (TIS) is a microscopic phenomenon and Karim et al (1976) recommend avoidance of this term on T staging but to include it in histopathological classification.

De Jong (1975) advocates considerations in T classification regarding horizontal and vertical spread of the tumor. Other possible improvements on the 1972 classification may be considered in the line of A.J.C. (1976) classification.

2 PRE–INVASIVE AND INVASIVE CARCINOMA

2.1 Pre-invasive carcinoma (Carcinoma in Situ: TIS)

The U.I.C.C. classifies pre-invasive carcinoma in the 3 major regions. It is practicable now to collect data on the pre-invasive carcinomas from the glottic regions as most publications appear to report pre-invasive lesions of only this region. Lederman (1970) records 104 pre-invasive carcinomas, out of which 97 are of glottic origin.

Only 6 cases of supraglottic pre-invasive carcinomas are reported by Smith et al (1973), out of a total of 1632 cases of carcinoma of the larynx, with 133 TIS carcinoma. Of these cases, 1060 are of glottic origin, of whom 127 are recorded to be TIS carcinoma.

It is emphasized that there is a growing trend to believe that the development of cancer in the larynx may occur following exposures to certain stimuli or carcinogens for a prolonged period. These stimuli may produce progressive and or reversible epithelial proliferative changes such as keratosis or keratosis with cellular atypia. Pre-invasive or carcinoma in situ changes may then follow in the laryngeal epithelium (Fig.1). Thereafter in certain locations at least micro-invasive cancers with or without frank malignancy may follow. This indicates that there may be areas of pre-invasive carcinomas side by side with frank carcinoma and either of them may be revealed by the biopsy specimen while the other is missed. Increasing incidences of concomitant presence of carcinoma in situ (TIS) at the vicinity of frank carcinoma are being reported (table II).

Therefore in a study on pre-invasive (TIS) carcinoma figures and numbers may mean little. However, pathologists, laryngologists and radiotherapists are becoming aware of the situation and while early literature hardly mentions TIS carcinoma of the larynx, recent ones are reporting increasing number of cases.

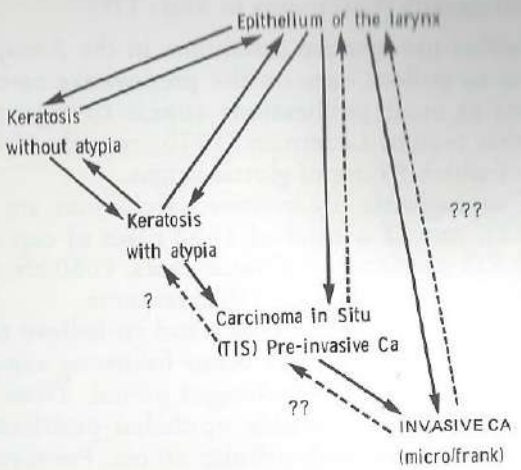
Table II

TIS (carcinoma in situ) concomitant with invasive carcinoma of the larynx.

Auerbach et al (1970)	100%	(post mortem cases)
Bauer (1974)	76%	(non keratotic cases)
Donner (1976P)	100%	(laryngectomy impressions)
Karim et al (1976)	55,4%	(radiotherapy patients)

From Karim et al (1976)

Fig. 1 Larynx carcinoma: TNM: TIS Carcinopathogenesis



Modified from Morrison (1971) with kind permission. The reversibility is indicated by question marks as contradictions exist on this topic.

Altman et al (1952) and Stout (1953), while describing 312 cases of carcinoma of the larynx, first have paid proper importance to this early malignant state. Stout reports radiation treatment of 5 patients with favourable results. He advocates multiple biopsies from apparently normal looking areas. These authors emphasize that the incidence of such lesions is not rare and report 29 true TIS carcinoma along with 19 others associated with frank carcinoma.

Lederman (1963) advises not to underdose these lesions while treating by radiotherapy and while he mentions of 21 keratosis and 58 carcinoma in situ, he emphasizes the presence of 74 cases where invasive carcinoma have been associated with keratosis, leukoplakia and pre-invasive carcinoma.

Fletcher (1964) reports 10 patients with pre-invasive TIS carcinoma while discussing 204 vocal cord invasive carcinomas. He mentions "Some of these 10 received irradiation over 5 years ago and the epithelium of the cords is still smooth". No dose response can be assessed. The overall dose in Fletcher's series is ± 1900 rets.

Hibbs et al (1969) reports 12 TIS cases along with 152 frank glottic cancer. He mentions of one TIS case with a fixed vocal cord. The patients have been treated with the same dose (± 1950 rets) as invasive carcinoma.

Delemarre (1970) undertakes a detailed study of 99 patients with proliferative lesions of the larynx and concludes, "It is impossible to really draw sharp lines between the classes II (squamous cell hyperplasia with atypia) and III (carcinoma in situ) and there always will be a subjective element in the diagnosis of a pathologist".

However, in spite of the small number of cases, 15% of class I (simple squamous cell hyperplasia), 23% of class II and 50% of class III non-treated patients with squamous cell hyperplasia of the larynx develop "malignant degeneration" in this series. Treatment details of class III (carcinoma in situ: TIS) patients are not possible to analyse from dose-response point of view from this study.

Lederman (1970) mentions 104 TIS patients while describing the histology of 1764 laryngeal carcinoma, an incidence of 6.0% . He puts emphasis on the adverse radiation response of frank cancerous lesions when associated with pre-cancerous states, such as papilloma, keratosis, hyperkeratosis and leukoplakia. He considers, "The radiotherapists' task in these circumstances may be made more difficult and the risks of complications increased, but cure by radiation is still possible".

Perez et al (1971) do not include 9 TIS patients while reporting 100 cases of frank carcinoma. All 9 are cured by radiation therapy. Dose is not reported.

Horiot et al (1972) mention 49 cases of pre-invasive carcinoma and 366 invasive carcinoma of the glottic larynx. Dose range is the same as in frank laryngeal carcinoma, ranging from 1828 to 2045 rets. Of these 49 TIS cases, there were 9.5% failures in "T1" group and 14% in "T2" group. In the radiotherapy-failure group, surgical salvage rate is 100%. It may be noted that "T1, T2 and even T3" pre-invasive carcinoma (TIS) does exist in the literature, as has been postulated earlier in this chapter and recorded by Lederman. This is paradoxical according to all the definitions (Karim et al 1976) of the U.I.C.C. (1972) and the A.J.C. (1976).

Smith et al (1973) record 133 TIS patients while describing 1499 invasive carcinoma of the larynx, an incidence of 8% . In an earlier report (1966), they could not mention one single case of pre-invasive carcinoma of the larynx out of 600 frankly invasive cases. They put emphasis on the fact that the TIS cases are becoming more frequently recognized. They describe 4 TIS cases as biopsy site error as they were clinically T3 or T4 laryngeal cancer. The cumulative 5 year survival is 97% in the "in-situ" group. Smith does not record details of radiotherapy but does give us full details of adopted treatment (Table III).

Table III

Treatment of 127 patients with in situ cancer who survived

Primary treatment	No.	No. with recurrences	Treatment of recurrent cancers
Radiation therapy	68	8	4 partial laryngectomy 2 total laryngectomy 1 total laryngectomy and neck dissection 1 neck dissection
Surgery	37	2	1 radiation therapy 1 total laryngectomy
Total laryngectomy	8	0	–
Laryngectomy and neck dissection	2	1	1 radiation therapy
Biopsy only	6	1	1 total laryngectomy
Stripping cords	3	0	–
Combined radiation therapy and surgery	3	1	1 surgery
Total	127	13	

From Smith et al (1973);
With kind permission of A.J.C. and the author (1976).

Goffinet et al (1973) record 8 TIS pre-invasive carcinomas out of 213 patients with carcinoma of the larynx, of which 146 cases are of glottic origin. But he does mention of sampling error and reports one patient with TIS staging who died of locally uncontrolled and wide-spread metastatic disease. It appears all other TIS patients are locally controlled by radiotherapy.
Jørgensen (1974) notices an incidence rate of about 8% for TIS (8 out of 102) in glottic carcinoma. Irradiation is found to be succesful in 6 cases and salvage surgery was succesful in treating 2 radiation failures.

There are few articles devoted solely to TIS carcinomas. Many of these articles are published after the Centennial Conference on Laryngeal Cancer in Toronto in 1974. While valuable information is available from the Conference on the subject of pre-malignant laryngeal lesions, it is clear that the concomitant presence of TIS and frankly invasive carcinoma is a real probability. Different considerations are stressed at the Conference by a panel of specialists e.g. definition, pathology, clinical appearance and management etc. It is concluded (Miller A.H. 1974) that at least on some points the pathologists could not agree with each other and with other panelists, in the same way as the therapists have disagreed on many aspects.

It is also clear that TIS carcinoma may affect a younger age group. Surgical procedures like stripping or cryosurgery with the aid of the operating microscope or even laryngo-fissure or laryngectomy are perhaps being used more frequently in some centres, particularly in the United States than in Europe.
There are however controversial viewpoints (Miller D., 1974) in support of radiotherapy, even in the U.S.A. In Great Britain and Europe, certainly a more conservative approach in favour of radiotherapy appears to be more accepted.
It is not possible from the literature to study dose response of these lesions.
In conclusion, further studies on the pre-invasive carcinoma of the larynx are needed for better understanding of this lesion.

2.2 The Glottic Carcinoma

Most publications on invasive carcinoma of the larynx describe T1 and T2 together as early cancer. Because of the ambiguity of the term early, frequent changes in the TNM classification and prognostic differences between T1 and T2 tumors, it is preferable to discuss each one separately. In a retrospective review, however, this may be difficult.
The T1 and T2 glottic lesions are most commonly treated by radiotherapy at least in Europe. The literature is vast and only a general overview may be possible in an attempt to comprehend the optimum treatment or the optimum dose-schedule.

2.1.1 T1 Glottic Carcinoma

Vermund's (1970) review reveals for this type of laryngeal cancers 86% 'relative' and 78% 'absolute' 5 year survival, following radiotherapy. Smith et al (1973) notice 94% survival (5 year) when the growth is limited to the site of origin (?T1a) as against 89% when the growth is limited to the region (?T1b) following primary radiotherapy.
These authors have published the results obtained from many institutes or publications. The collections deal with a huge number of patients treated relatively contemporarily.
Lederman (1963, 1965, 1970, 1974, 1976P) on the other hand, publishes results of his personal experience, also with a huge number of patients over decades. Lederman's vast work gives us a clear insight into the evolutionary aspect of radiotherapy of laryngeal carcinoma in a mixed era of development. His 2 years survival rate is above 85% including all the patients over the whole period.
All publications indicate the high rate of success of radiotherapy when the tumor is small.
Some authors, more appropriately, have utilized 2 or 3 years recurrence-free local control rate (No Evidence of Disease locally - NED) as the yardstick instead of the conventional 5 year survival. When the parame-

ter is 2 years recurrence-free NED, the success rates of most recent publications are above 85% for T1NOMO glottic carcinoma with radiotherapy. The idea of dose response (higher control rate with higher dose) is initially indicated and experimented by Morrison et al (1962). He obtains dose response for overall glottic lesions.
The same trend is indicated (but not explicitly mentioned by all) by Perez et al (1971), Aristizabol et al (1972), Goffinet et al (1973), Vaeth et al (1972), Marks et al (1973) and Fayos (1975).
The other group led by Fletcher et al (1964, 1970, 1974) denies the presence of dose response for early glottic carcinoma. This group includes among others, authors like Stewart (1964, 1969), Hibbs et al (1969), Horiot et al (1972) and Jørgensen et al (1971, 1975, 1976P). Some believe that higher dose invites more complications without increasing the local control rate (Stewart 1969). Many others do not try to obtain dose response in their series. The control probability, the controversies on dose response, treatment schemes etc. of some authors are summarized in table IV.

Table IV
Publications on Early Glottic Carcinoma
Old T1 (= T1a, 1972 U.I.C.C.) tumors. (1962-1973)

Author	Year	Control rate average %	Dose-response for cure	Remarks on treatment scheme
Morrison	1962	66-89*	obtained	protracted (all stages)
Fletcher	1964	90	not obtained	protracted & short
Stewart	1964	96	indicated by the study but not specifically described	short scheme
Baclesse	1967	88		protracted
Chahbazian	1967	96		short
Hibbs	1969	92		short
Stewart	1969	90	not obtained for cure but indicated for complications	short
Lederman	1971	85		protracted
Horiot & Fletcher	1972	88	not obtained	protracted and short
Aristizabol	1972	40-75-100*	obtained in a very small series	convincing review with Protracted fractionation
Abramson	1973	88-90*	not obtained	2 different fractionation schemes used
Marks	1973	75-79-86*	obtained both for cure and complication but considers the flat upper sigmoid part of the dose response curve.	protracted

Many authors have not attempted dose response.
* Different dose schemes were used with different local control rates.

Some recent publications have utilized the 1972 TNM classification with more precisely recorded pre-treatment parameters. (Table V). In these recent publications, Fayos (1975) obtains dose response for T1 glottic carcinoma, Jørgensen et al (1974, 1976P) deny its presence and others have not mentioned this important point. In personal communications, however, Eschwege (1976P) denies the presence of dose response for a group of patients with early glottic carcinoma.

Table V
Recent publications on early glottic carcinoma

Author	Year	T/TNM UICC '72	Control-rate or probability %	Dose-response	Remarks on treatment scheme and others
Sony et al	1974	T1	83	Not attempted	Protracted with electrons
Wang	1974	T1a	94	Not attempted	? TIS included. Protracted fractionation scheme
		T1b	82		
Jørgensen	1975	TIS	75		
		T1a	82	Not obtained	Short scheme
		T1b	72		
Eschwege et al	1974	T1a	82	Not obtained	Protracted
		T1b	60		
Fayos	1975	T1	90	Obtained	Protracted
Stewart	1975	T1	90	Not obtained	Short

Table VI
T1 Glottic carcinoma: 3 years local control rates
Influence of extent and site of the tumor.

T classification or site	Probability of control %	Number of patients
T1a (anterior 2/3)	94	240/255
T1b (but only anterior parts)	82	46/56
Posterior third (T1a) or entire cord	75*	70/93
	88	356/404

Modified from Wang (1974) with kind permission (1976P)
*The worse prognosis of tumors affecting posterior parts of the cord or one entire cord although classified as T1a is to be noted.

Wang (1976P) like many others, does not practise varying doses, to be able to comment on dose response. He (personal communication 1976) notices, "The control rate is directly related to the stage of the disease with a dose value of 1875 to 1900 rets". This perhaps leaves an impression on the scope of dose response for larger tumors, but nothing more may be construed. His experience with huge patient material is invaluable particularly in understanding the prognostic influence of the extent of the tumor. This is not commonly realised (Table VI) for T1 tumors.

Reliable data retrieval from old literature is possible only on T1a glottic carcinoma. The high rate of control is obvious but may be marred by the incidence of complications. Thus is appears advantageous to consider complications here as rigid parameter is possible to follow on the primary tumor. Although any considerations of major complications should distinguish between persistent severe edema and necrosis, it is difficult to retrieve these from the literature separately. Hence dose response for complications in this study would indicate overall major complications. One may have reservations in indicating persistent edema as a major complication, considering that the edema may disappear after a variable period. In many papers overall complication rates have been omitted or lumped together for all (T) subgroups. Therefore, only an overview may be obtained from past publications.
The names of the various authors have been plotted with the control (at least 2 years NED) probability, dose in rets used by the authors and the maximum reported complication rates in Fig. 2, 3 and 4.

Figure 2 T1a Glottic Carcinoma (one mobile V.C.)
Average ret dose as a function of the local control probability and the names of the authors using protracted or short treatment schemes. Control rates above 80% may be obtained with different doses and schemes. No dose response is indicated beyond a reasonable high dose.

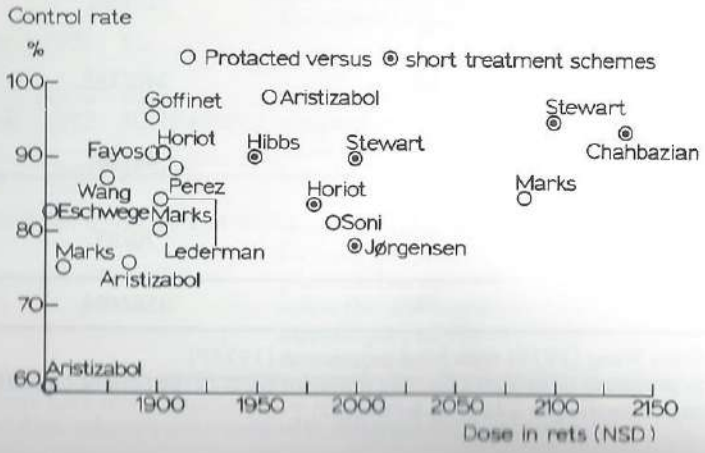


Figure 3 T1a Glottic Carcinoma (one mobile V.C.)
Maximum complication rates as a function of ret doses used by various authors in protracted or short treatment schemes. Dose response for complications indicated for short schemes, while the complication rate for the protracted scheme is rather constantly low.

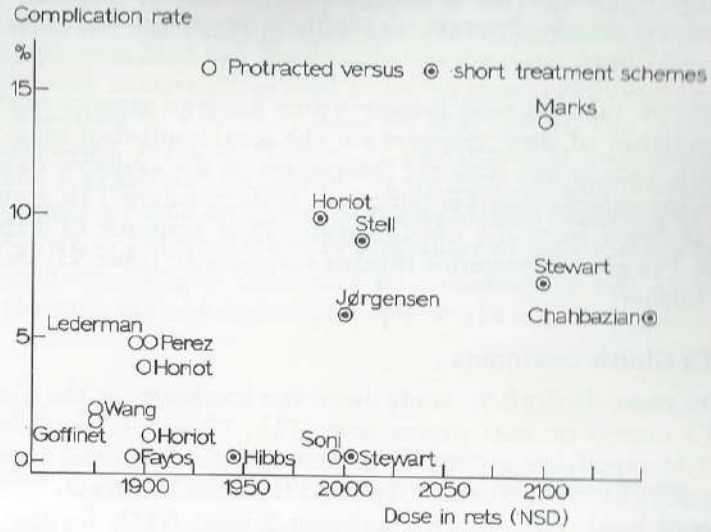
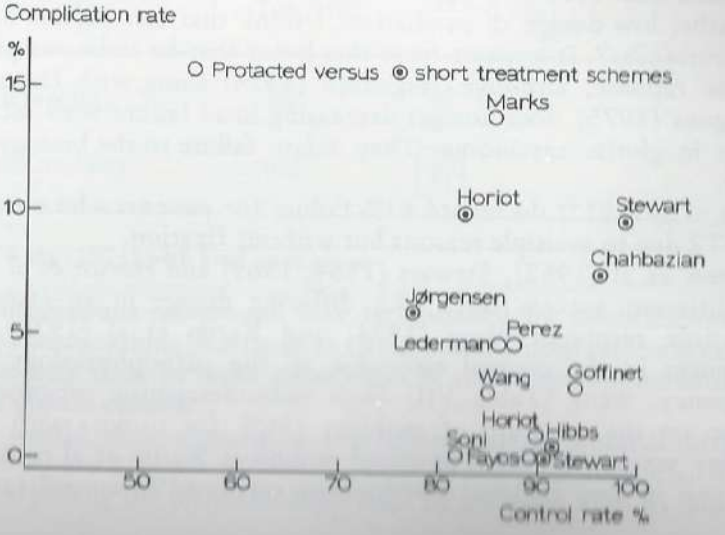


Figure 4 T1a Glottic Carcinoma (one mobile V.C.)
Maximum complication rates and the control probabilities in short versus protracted treatment schemes.
Higher complication rates for short schemes are evident although the control probabilities remain unchanged.



The maximum possible complication is recorded as the rate mentioned by the authors for all T subgroups. This has been assumed to be the same for the T1 category although in practice it should be much less. High dose short treatment schemes resulting in high ret values do not appear to have improved control rates, but induce higher complication rates (Fig. 3 and 4). This is already pointed out by Fletcher (1964, 1970, 1974), Scholte (1974P) and Ellis (1975P) and Stewart (1969, 1974P).

The literature then, in most instances does not lend support to the idea of the presence of dose response for the local control of most of the T1a glottic tumors but with the limitations of the available data, dose response for complications is indicated. Unfortunately T1b group cannot be analysed from the old literature. Dose response of T1b and a high risk T1a group (posterior third or entire cord: Table VI) should be studied further.

2.2.2 T2 Glottic carcinoma

These are more difficult to study from the literature, as the old (1962 TNM) T2 tumors in most papers cover T1b, T2 and T3 carcinomas of 1972 TNM classification (see 1.1). One may get a general impression on the results of the treatment (figure 5) from the literature.
The overall local control rate (minimum 2 years NED) for the old T2 glottic carcinoma is about 60 to 75% . Perhaps T1b and T3 tumors have balanced each other's influence on the prognosis, as in the most recent publications a similar local control rate is noticed. Exceptions are recorded by Jørgensen (1974) with a rather low figure of 44% and by Horiot (1972) mentioning 39% for a selected T2 group. Jørgensen explains (personal communication 1976), "The T2 group is not a very optimistic one. From the paper included, you can see that our patients had rather low dosage of irradiation. I think that can explain some of the recurrences". It appears from this letter that he indicates presence of dose reponse, although Jørgensen (1974) along with Hansen and colleagues (1975) does not get decreasing local failure with increasing dosage in glottic carcinoma. They relate failure to the biology of the tumor.
Horiot et al (1972) do record 61% failure for patients who were designated T2 due to multiple reasons but without fixation.
Morrison et al (1962), Stewart (1964, 1969) and Horiot et al (1972) give different success rates with differing dosage in an attempt to elicit dose response. Wang (1974) and Karim et al (1976) record differences in the control rates due to the pathophysiology of the malignancy. Wang (Table VII) finds radiotherapeutic prognostic difference on the question of mobility (86% for tumors with normal mobility versus 63% with impaired mobility). Karim et al record (72% with one or two regional involvement versus 61% control rate with

transglottic involvement) prognostic differences on the volume of the tumor (e.g. transglottic spread) as an important factor. Certainly both these factors or combinations influence the outcome of radiotherapy. Smith et al (1973) record only 21% 5 year survival rate in the true transglottic (more tumor mass) growths when treated by radiotherapy, against 67% when treated by surgery. Although Smith like Lederman attaches great importance to fixation, the above figures do not indicate how many patients have had fixed cords. On the other hand 76% of the true transglottic tumors are proved to be T4 due to extra-laryngeal extensions according to a series by Kirchner et al (1974). The importance of the pathologic mass or volume of the tumor in radiotherapy is known, but a pragmatic therapeutic approach is seldom documented. The importance of such an approach is emphasized (Karim et al 1976) when one tries to pinpoint the causes of failure of radiotherapy in glottic T2 carcinomas. Higher dose may be considered if one has to implement the basic radiobiological principles in the clinics.

Table VII

T2 Glottic carcinoma: Local control rate at 3 years.
Extensions & Normal mobility versus Impaired mobility in parenthesis.

Extensions	Local control %	numbers
T2 supraglottic	84 (52)	$\frac{36}{43}$ $\left[\frac{12}{23}\right]$
T2 subglottic	89 (0)	$\frac{16}{18}$ $\left[\frac{0}{2}\right]$
T2 transglottic	100 (100)	$\frac{4}{4}$ $\left[\frac{2}{2}\right]$
Normal mobility	86	$\frac{56}{65}$
Impaired mobility	(63)	$\left[\frac{32}{51}\right]$

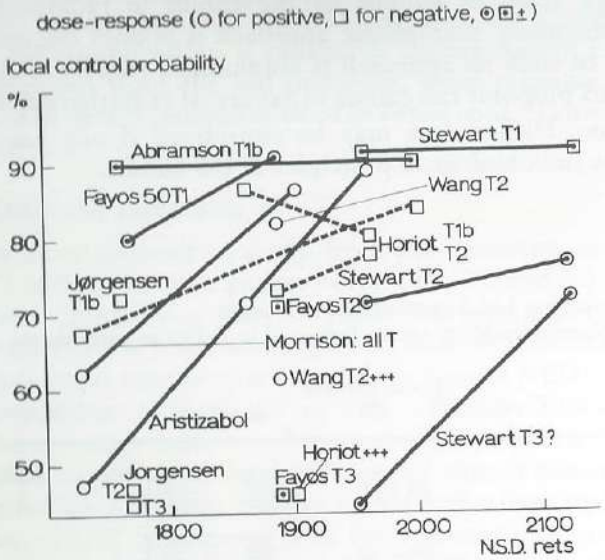
From Wang (1974) with kind permission

More homogeneous sub-groups may be obtained by modifications of the TNM classifications (Karim et al 1976) and the dose response experimentation may then be more meaningful in the subgroups particularly of the T2 glottic cancers.
In other words, dose response in this heterogeneous group is difficult to study. Figure 5 shows the controversy on the dose response. While some lines joining the different doses used by different authors indicate

rather definite dose response, others indicate the flatness of the response to the increasing dose. It must be noted that most publications are on the old T2 (1962) classification except the ones from Wang (1974), Fayos (1975), Jørgensen (1975) and Stewart (1975, 1974P).

Figure 5 Glottic Ca Old T2 (1962) 1972: T1b, T2, T3

The names of the authors are plotted with the ret doses used and the control probabilities obtained. Multiple dose systems used by the same author have been joined by indicator lines to reveal dose response controversy.



+++ indicates high risk group (T2 due to multiple reasons).

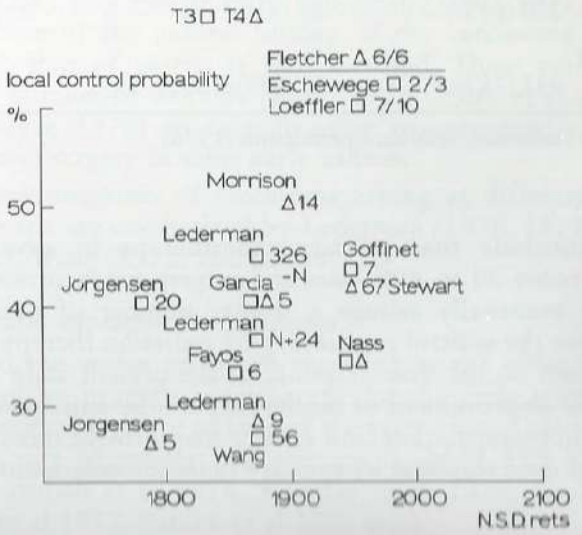
2.2.3 The advanced glottic carcinoma

Information on radiotherapy of T3 glottic carcinoma is scarce and difficult to retrieve from the literature because of the factors previously mentioned. Moreover, in many centres surgery is the preferred mode of treatment. In many papers T3 tumors are frequently mixed up with T4 and together are termed advanced tumors, not an ideal set-up for retrieval. These advanced tumors are also recently and perhaps increasingly being treated by a combined approach (Goldman et al 1970, Hendrickson 1970, Kazem et al 1975, Hordijk 1977).
Low or high dose pre-operative radiotherapy is being used in many centres, followed by surgery. To determine the optimum, a number of controlled randomized trials is needed before valid conclusions may be

reached. Basically the advanced tumors are more difficult to manage successfully by primary radiotherapy. Infiltration of cartilage or bone, large mass of tumor with more hypoxic foci, edematous stroma, regional metastasis etc. are some of the factors contributing to radioresistance.

The usual advanced age and low general condition of many patients suffering from chronic cardio-vascular or lung diseases, low ebb of immune defence system, presence of micrometastasis and a host of other factors may further complicate the outcome. Even then the success rate with primary radiotherapy, in some publications, is not very low (figure 6). The probability of higher control rate with acceptable incidence of complications may be explored with higher doses if one wishes to accept a more conservative approach. Presence of dose response must be a pre-condition to such an approach. Clearcut indication of presence of dose response in advanced glottic carcinoma is difficult to obtain from the literature except Morrison et al (1962) and Stewart (1975). Recent experiences are urgently needed. The available information may be overviewed in figure 6. It appears that only few authors have used dosages beyond 1900 rets and these few have recorded reasonable control rates.

Figure 6 Advanced glottic carcinoma with fixed cord and/or extralaryngeal growths.



The numbers indicate total number of patients. With small numbers of patients Fletcher, Eschwege, Loeffler record outstanding control rates in selected groups (see subset at top right). Others record 25 to 50% control rate in advanced glottic carcinoma. Few except Fletcher, Stewart, Loeffler, Goffinet and Morrison use higher dose.

Some authors (Lederman 1965, 1970, 1974, Bryce 1972) are persistently preaching for more conservatism for (Table VIII and IX) patients with advanced laryngeal carcinoma. There is perhaps a lumping of the patient material in these tables but the message that more voices are preserved by a conservative approach is clear. Pre-operative radiotherapy is increasingly being found to be of no further benefit in advanced glottic cancers in some recent literature (Hendrickson et al 1970, Kazem et al 1975, v.d. Brock et al 1977).

Table VIII

Larynx carcinoma: Comparison of results of treatment by surgery & radiotherapy

Royal Marsden Hospital		Royal ENT Hospital			
RT	RT +	RT	RT +	Primary surgery	
Alone	Salv.Surg.	Alone	Salv.Surg.	Alone	with RT
372	115	108	44	125	16
(487)		(152)		(141)	
stage					
287 I & II				(293)	
				stage	
200 III & IV				249 I & II	
				44 III & IV	
Survival					
Overall 5 yrs.	308 (63%) --------	93 (61%) ----------		90 (64%)	
with					
Intact Larynx	241 (78%of 308) ---	70 (75%of 93) -------		0	

Modified from Lederman with kind permission (1976)

One may conclude that primary radiotherapy in advanced glottic lesions may recue 30 to 40% cases and surgery for recurrent or residual growth may eventually salvage a similar number of patients. Nodal disease reduces the control probability by radiation therapy.
Little is known on the dose response at the present state of knowledge. As further improvement of results may not be anticipated from pre-operative radiotherapy, time and energy may now be directed to study the aspects of dose response by primary radiation treatment.

Table IX

Advanced (T3 and T4) Laryngeal Carcinoma: Multiregional, extralaryngeal, fixed cords with or without nodal metastasis:

Treatment results: A Surgeon's View.

Treatment	No. of Patient	3 yrs. Crude Survivors	No. of Patients with intact Larynx
Pre-operative Radiotherapy and Surgery	52	52%	0
Primary Surgery	23	48%	0
Primary Radiotherapy and Salvage Surgery	98	58%	42

Modified and with kind permission from Bryce (1972)

2.3 Supraglottic Carcinoma

The supraglottis is a relatively extensive area and many controversial viewpoints exist on the treatment of supraglottic carcinoma with possibilities of differing natural history of these growths. The anatomic and the pathophysiologic differences of the supraglottic area as compared to that of the glottic region are detailed in almost all textbooks and amongst others very precisely by Lederman (1970, 1971, 1974, 1977). The difference of the natural history of the carcinoma of the supraglottis with that of glottis is well focussed. These perhaps have encouraged a number of workers (Bocca 1975, Ogura et al 1970, Biller et al 1970, Bryce 1972) to take recourse to conservative (supraglottic laryngectomy) surgery in some early cancers.

The different prognosis of carcinoma arising at different sites within the supraglottis are emphasized by Lederman (1970, 1971, 1977), Morrison (1971), Wang (1973) and others.

2.3.1 The early supraglottic carcinoma

Contrary to the worse prognosis recorded in the older literature, the local control by primary radiotherapy for the early growths is almost similar in recent literature to that of the early glottic cancers. In general, the success rate of proper radiotherapy is above 85% (Morrison et al 1962, Nematullah et al 1974, Fletcher et al 1970, Shukovsky 1970, Deffebach et al 1972, Bataini et al 1974 etc.)
Presence of dose response in early supraglottic carcinoma is either demonstrated or indicated (Morrison et al 1962, Baclesse 1967, Shukovsky 1970, Deffebach et al 1972, Goffinet et al 1973, Bataini et al 1974, Nematullah et al 1974 and others) in almost all series.

The critical range of the optimum dose along with the steepness of the dose response curve is clearly pointed out by Shukovsky (1970) for T2 and T3 supraglottic tumors, in particular.
Many authors do not practice changing dose systems to comprehend the dose dependence of the supraglottic tumors. Even then it is clear that controversy in dose response does not virtually exist in the field of early supraglottic carcinoma.

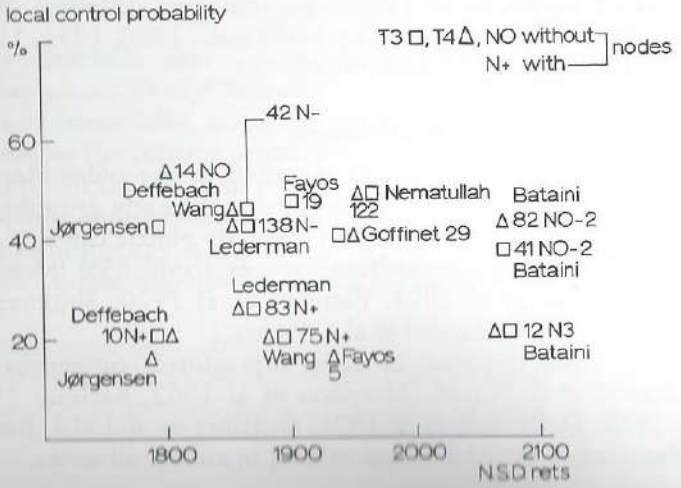
It may be assumed therefore that cautiously utilized higher dose of radiotherapy increases the rate of local control of the early supraglottic laryngeal carcinoma with acceptable complications of a minor nature.

2.3.2 The advanced supraglottic T3 and T4 carcinomas

Few publications on primary radiotherapy of these tumors indicate that many of these patients are treated by surgery or by a combined approach (Ogura et al 1965, Goldman et al 1970, Hendrickson 1970, Fletcher 1973, Cachin et al 1975, Kazem et al 1975). Many of the tumors may be radioresistant due to hypoxic areas in bigger tumor volume, stromal characters, cartilage and nodal involvement, failure of immune competence etc. At the same time we should be vigilant not to follow the 'easy tracks' to save life and yet deprive someone of his capacity to speak. A number of recent publications show reasonable results of primary radiotherapy for the advanced supraglottic growths (figure 7).

Figure 7: Advanced supraglottic carcinoma

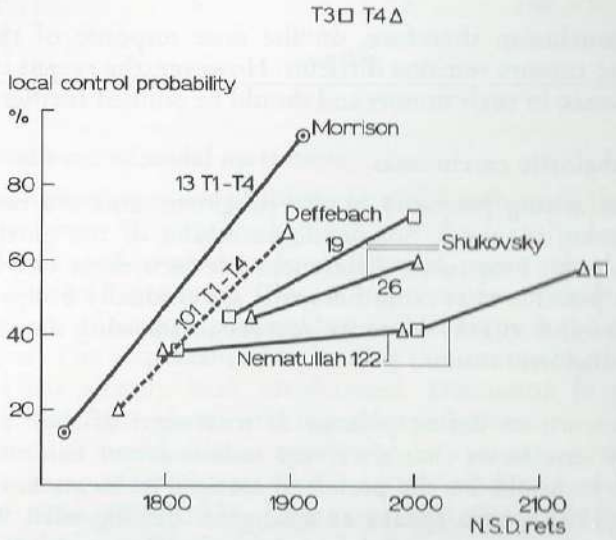
Results of radiotherapy in advanced supraglottic carcinoma with or without nodal disease. The total number of patients is indicated along with the control probability and the ret doses used by the different authors.



These experiences by researchers in the field indicate that in certain situations, the effects of radiotherapy may not be as dissatisfying as is commonly thought for supraglottic advanced laryngeal carcinoma. If this is substantiated in future, exploitation of the dose response curve may improve the results still further. In general this statement may be true for T3 tumors (Shukovsky 1970). Few papers reveal dose response in advanced supraglottic malignancy (figure 8). Metastatic nodal disease complicates the issue.

Figure 8:

Dose response in advanced supraglottic larynx carcinoma.



Different dose points used by the various authors are joined by lines to indicate the slope of the dose response.
Shukovsky's group of T4 tumors and Nematullah's T3, T4 groups indicate relatively flat response.
Numbers indicate total number of patients.

The presence of dose response in T4 supraglottic tumors is scarcely recorded but the success rates are high according to some authors, above 40% in 50% of the papers when the nodes are not present or not fixed. Lowest success rates (20%) are scored by Fayos (1975) and Bataini et al (1974). The patients with such bad prognosis are recorded to be with fixed nodal disease by Bataini et al.
It may be possible that better definition, subgrouping and selection of T4 supraglottic tumors, along with the exploitation of the dose response concept and improved technique of radiotherapy as well as of surgery may increase the local control and the survival of the patients with

advanced tumors with no further increase in complication rate. Salvage surgery or surgery for the nodal disease may remain as standby. These speculations, if found to be true, may allow more patients to retain their voices. If this is not sustained, results obtained by combined method of treatment must be preferred. Kazem and his colleagues (1975) obtain a very high (88%) control rate in advanced supraglottic laryngeal carcinoma by a short intensive course of pre-operative radiotherapy.
Fletcher et al (1970, 1974), report 71% survival at 2 years with post-operative radiotherapy compared to 38% with surgery alone. Cachin et al (1975) review all the literature on combined approaches and conclude in favour of post-operative radiotherapy.

Definite conclusion therefore, on the dose response of the advanced supraglottic tumors remains difficult. However, the recent trend indicates its presence in such tumors and should be studied further.

2.4 The subglottic carcinomas

Carcinomas arising primarily in the subglottic area are rare and only recently being focussed. Subglottic extension of the glottic tumor is rather common. Prognostic differences between these two groups may exist. It is possible that radiotherapists see gradually disappearing gross tumor mass and so may be more correct in assessing the site of origin of a true subglottic tumor.

Little is known to define policies of treatment of such rare tumors. Frequently one hears that these are radioresistent tumors and therefore surgery should be the preferred method of treatment. According to Bryce (1972), who speaks as a surgeon dealing with 923 patients with laryngeal carcinoma, the prognosis of patients with the subglottic carcinomas is poor and independent of the modality of treatment. He considers that it is not yet definitely established whether surgery or radiotherapy should be the primary preferred method of treatment. He warns that extensive paratracheal and mediastinal nodal dissection may have to be carried out for gross tumor with nodal masses. One should plan treatment keeping this in mind.
It is difficult to retrieve old literature for the rare subglottic tumors but when accomplished, one does not know whether the important points raised by Bryce (1972) have been already considered for therapy. Nor is it known how efficiently radiotherapy has been applied. Therefore one may expect better results either by surgery or by radiotherapy or by a combined approach in future if high and comparable quality of treatment is planned. In radiotherapy little is known on the dose response of the tumor at the subglottic site. However, radiotherapy may be one effective (table X) way of treatment.

Table X:
Subglottic Larynx Ca: All Stages
Results with Surgery & Radiotherapy (RT)

	Total pts.	RT : Surgery	%Control probability RT : Surgery
Vermund (1970)	185	127 : 58	36 : 42
Smith (1973)	19	8 : 10	62 : 40
Lederman (1970)	140	All by RT only	44 :
Jørgensen (1974) (with low doses)	9	4 : 5	0 80 (2 cases treated combinedly)
Iwamoto (1975P) (all females)	6	4 : 2 (incl. one T4)	100 : 0

2.5 The treatment of nodal metastasis.

The glottic lesions pose less problems in nodal metastasis than the supraglottic carcinomas. The rare subglottic growths may be less metastatic in the neck but tend to produce lower cervical, paratracheal and superior mediastinal nodal metastases. Clinical impressions on nodes at the subglottic site, are difficult to assess when radiotherapy is the only method of treatment. The importance of planning the treatment of the subglottic lesions has already been emphasized. Discussion in this chapter therefore is limited to glottic and supraglottic lesions.
The incidence of nodal disease appears to be constant over the year in the glottic area. Most figures indicate an incidence of less than 4% (Lederman 1965, 1970, 1975, Jørgensen 1970, Snow 1970, Maw 1975) However, varying incidences of nodal metastasis are reported in the supraglottic carcinoma. Perhaps the least is reported by Maw (1975) who found 20.5% nodal metastasis in 229 patients. The average of 36.9% is reported by Lederman (1970) in 507 patients. In the maximum range come Bataini et al (1974): 47% out of 218 cases, Lindberg (1972): 55% in 267 patients and Bryce (1972): 67% in supraglottic carcinoma. Obviously the incidence will depend mostly on the extent of the primary disease and the histological grading (Snow 1970). Bataini notices that his high figure of nodal incidence (47%) was largely due to 40% of all his patients having T4 lesions at presentation.
There are controversies on the treatment of the nodal disease amongst radiotherapists.
Many think that up to a certain extent (e.g. neck nodes up to 3 cm diameter), the tumor in the neck may be manageable by radiotherapy (Fletcher 1973, Lederman 1970, Maw 1975).
On either side of this attitude, there exist the extremists. The conventional group of radiotherapists considers that the nodal disease is more

radioresistant and therefore surgery is to be preferred. Historically, perhaps, this attitude has evolved from the treatment methods used over many decades particularly in head and neck area when much higher dosage (specially with the low dose rate of interstitial radium) was usually delivered on a circumscribed primary tumor, leaving the secondary nodal area to be treated by the much less efficient orthovoltage radiations. On the other side of the scale, there are proponents for radiotherapy for metastatic carcinoma in all stages (Dobbie 1954, Bataini et al 1974 and Henk 1975) with nodal disease. They find that their figures lend no support to the idea that secondary carcinoma in lymph nodes is more radioresistant than the primary. Henk feels strongly that the old concept should be discarded. However he concludes that the choice of treatment lies between radiotherapy alone and a combination of surgery with radiotherapy.
Bataini et al (1974) almost reach a similar conclusion by delivering more than 9500 rads to the nodal disease to get more than 40% success rates in N1 and N2 diseases (with T1 to T4 supraglottic carcinomas). His success rate for fixed (N3) nodes is around 15% . He concludes in favour of neck irradiation for nodal metastasis with limited surgery being reserved for the management of residual disease - a policy discouraging radical neck dissection in these patients.
From these publications, it appears probable that high dose radiation, if properly planned may sterilize a larger number of lymph nodes than is usually conceived. This may be true for tumors of smaller volume.

2.6 The distant metastasis (M1)

Most distant metastases are associated with advanced local disease and/or virulant tumors. They have a poor prognosis and are fatal within a short period. Most series therefore exclude these cases in survival or dose response studies, particularly when treatment methods are evaluated. Fortunately, however, their numbers are very small.

3 OTHER PROGNOSTIC FACTORS

The extent of the primary (T), the nodal tumor (N) and the presence of distant metastasis (M) influence the prognosis most. These have been discussed in chapter 2. The histological differentiation or grade, although known to be important in determining the prognosis of a tumor has unfortunately not been studied in most publications. The natural history of a particular tumor may not only depend on the histological virulence but also on its dynamic interaction with the usually unassessable host defence mechanism. The efficacy of the treatment methods shall profoundly influence the outcome. Few other factors may be considered.

3.1 Sex of the patient

Lederman (1965, 1970, 1971) has recognised the better prognosis in females to such a degree that he advocates radical radiotherapy for all female patients irrespective of the TNM staging of the tumor.
Many publications do not mention this point. Coutard (1932) noticed 60% control rate in females as against 16% in males in malignant tumors of the laryngo-pharynx. An attempt to gather information on this topic has been reasonably successful by personal communications with the authors treating patients of diverse nationality. Without the cooperation of these authors, the compilation of table XI could not have been possible. This table, in the international context, appears to prove the contention of Coutard and Lederman that females do better than men when afflicted with laryngeal carcinoma. The control probability in females appear to be around 70% compared to less than 50% in males.

Table XI

Carcinoma of the larynx: Difference of Survival in Males and Females

Author	No. of Patients Male	: Female	Control probability % Male	: Female
Lederman (G.B.)	1345	150	46	57
Tsvetkov (USSR)	92	113	48	71 (orthovolt)
Wang (USA) (Supraglottic)	146	38	59	76
Jørgensen (Denm.)	152	16	68	88
Fayos (USA)	174	18	'Prognosis better in females'	
Iwamoto (Japan)	5757	603 (for each stage)	±45	± 58
Total	7666	938	± 45	± 68

Iwamoto (1976P) indicates that the prognosis is better in females in each local and regional staging. However both from Japan and from Moscow the relatively worse prognosis in females with nodal disease is stressed.

3.2 The histological surprises

The adenocarcinomas of the larynx, carcino-sarcomas, sarcomas of various sorts, lymphomas, oatcell and verrucous carcinomas, melanomas etc. are all very rare growths but they do occur. It is probable that most of the above lesions are radioresistant and may tell upon the control rate, particularly when dose response is the important consideration. In the Mayo Clinic material of 30 years, only 6 cases of adenocarcinomas are described (New et al 1941) out of about 1300 laryngeal malignant tumors. None of the six was radiocurable. Verrucous carcinomas are recently encountered as radioresistant lesions with a tendency of perineural spread (Nostrand et al 1972, Demian et al 1975). These tumors have not been studied from the dose response point of view. Collaborative studies are needed in this field.

3.3 Host immune defence

The role played by host defence mechanism in control of the tumor may be important and must be dynamic. The interactions of the host defence mechanisms against tumor may be altered by treatment. The basic methodology and technical know-how of studies on such interactions are yet ill-understood. Some in vitro studies have been appearing recently. Accurate in vivo studies are difficult to plan.

Radiations, as is usually thought, may be immunodepressant in patients with cancer in other localities (Stjernsward et al 1972). Controversies on this point do exist not only on radiotherapy (Karim 1976, 1976), but also on chemotherapy (Hersch et al 1974). It appears that a state of immune tolerance may sometimes be broken by radiations or chemotherapy. The high cure rate of laryngeal carcinoma with radiotherapy alone may be indicative of this. However, dose response in relation to such unknown parameters, although important, may be impossible to study at the present state of knowledge.

4 COMPLICATIONS

Prohibitive complication rates were noticed by early workers. Gradually with experience, technical improvement, high quality radiations, good dosimetry etc., the complication rates have been brought to the minimum.

Even then they have not totally disappeared. In some studies the rates appear to be quite high: 5 to 15% . One tends to get higher complication rates in an attempt to minimize the local recurrence rate. The concept of narrow optimum dose range for cure of laryngeal carcinoma and increasing complication rate along with higher cure rate, particularly for early carcinomas of the larynx is discussed by Moss et al (1973). They conclude that it is now obvious that where high dose irradiation is necessary for the cure of laryngeal carcinoma, the dose producing maximum cures is very near the dose producing prohibitive sequelae. This is schematically represented in figures 9 and 10.

Figure 9
Increase of complication-rates after the optimum cure-rate is reached

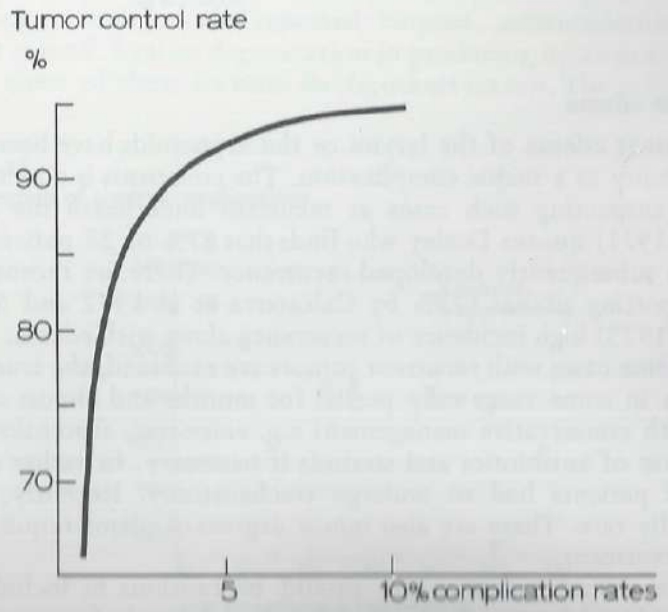
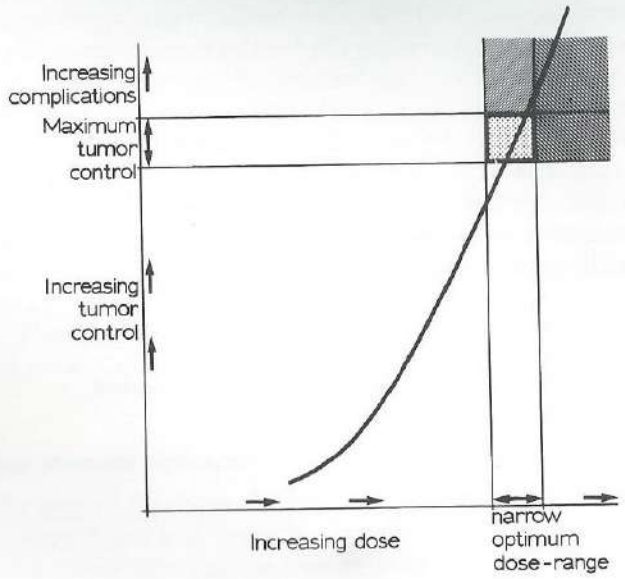


Figure 10
The concept of dose response in relation to narrow optimum dose-range and complications



4.1 The late edema

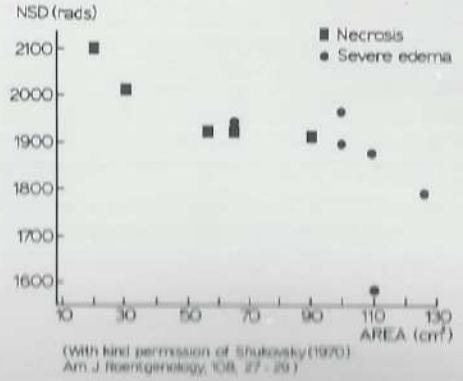
Late persistent edema of the larynx or the arytenoids have been considered by many as a major complication. The consensus is now more in favour of suspecting such cases as recurrent underneath the edema. Morrison (1971) quotes Deeley who finds that 87% of 38 patients with late edema subsequently developed recurrence. There are recent publications reporting similar (73% by Calcaterra et al 1972 and 50% by Ward et al 1975) high incidence of recurrence along with edema.
If these edema cases with recurrent tumors are excluded, the true laryngeal edema in some cases may persist for months and almost all may subside with conservative management e.g. voice-rest, abstention from smoking, use of antibiotics and steriods if necessary. In earlier days, a number of patients had to undergo tracheostomy. Recently, this is exceptionally rare. There are also minor degrees of edema requiring virtually no treatment.
From these points of view, one should be cautious in including all radiation induced laryngeal edema under the sub-head of major complications.

The volume of irradiated tissue plays an important role and has been well-focussed by Shukovsky (1970) amongst others. The most outstanding work on late edema in relation to dose is by Kok (1971). Recently an extensive analysis have been completed by Kok (1977P) and colleague showing the relevance and advantages of different mathematical models for obtaining the norm doses in radiotherapy (see preface) in relation to laryngeal edema (Westermann et al 1977).

4.2 Necrosis

Necrosis of any part of the irradiated larynx is a major complication and perhaps should be separated into areas e.g. cartilage, soft tissues, skin etc.. Few papers have been published on necrosis alone (Stell et al 1973). Reportedly the necrosis rate varies around 6% , but in recent publications the incidence of necrosis is rarely found, perhaps due to improved knowledge, technique and availability of supervoltage radiations, prolonged fractionation, etc.
Protracted fractionations or increase in the total period of radiotherapy appear to reduce necrosis rate and are advised by many (Fletcher 1964, 1970, 1974, Stell et al 1973, Scholte 1974P and Ellis 1976P). This is indicated in chapter 2 (figures 3 and 4).
The overall incidence of major complications may in general be said to be historically associated with 3 factors: orthovoltage irradiation, large volume of treatment and short treatment period delivering a relatively large daily dose. The role of the total cumulative high dose, infection, smoking, trauma of the repeated biopsies, arteriosclerosis, vascular tumor emboli, hyaline degeneration in producing necrosis etc. are noted. While some of these are remediable, others are not. The volume of treat-

Figure 11
Scattergram of severe complications



ment and in particular, avoidance of the arytenoid area in relatively anterior tumors have been under attention of Fletcher, Ellis and Shukovsky amongst others. A Scattergram has been constructed by Skukovsky (1970) to show the effect of volume on laryngeal oedema and necrosis in supraglottic cancers (figure 11).

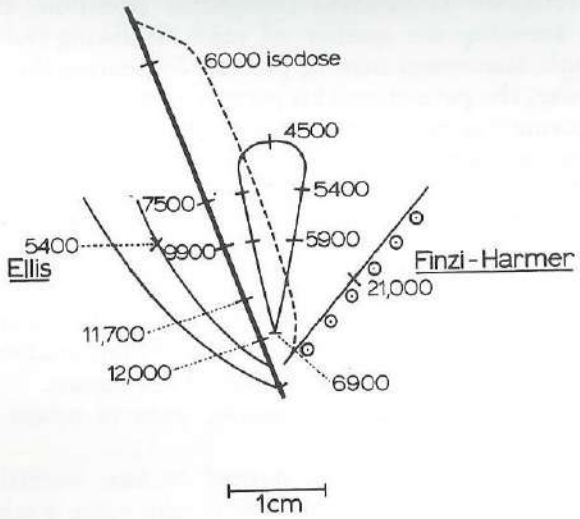
5 THE VOICE

This is an important consideration but unfortunately has received little attention in the literature. Pioneering work of Finzi (1928), mentioned previously (chapter 1) deserves thoughtful attention. Objectivity is difficult in assessing the quality of voice following radiotherapy. In general, simple assessment may be possible by scoring the assessment of the interviewer, the patient and his partner or near relatives. Unfortunately such scoring has rarely been practised, perhaps as improvement of voice is more or less taken for granted. Some publications (Hibbs et al 1969), Marks et al 1971, Stoicheff 1974, Mendonca 1975) have focussed recently on this topic in relation to radiotherapy. Much more work has been done with surgical patients and the attention of radiotherapists is drawn to this fact. Scholte (1954, 1974P) has investigated a few patients as these patients have had a sonoric voice following radiotherapy, which had appeared to themselves and/or their relatives better than their normal voice years before the onset of the disease.

There are a few records of such events, even in recent publications (Marks 1971, 1973).

Usually the voice is improved to normal or near normal in most instances. In one study by Stoicheff (1974), the voice is normal in 45%, near normal in 39% and little improved in 15%, following radiotherapy. Usually the voice tires easily. This may be a problem to singers, lawyers, public speakers, teachers etc.. To solve this particular problem, Ellis (1975, 1976P) has devised a brachytherapy plan of treatment. Few patients have so far been treated, but the results are reported to be excellent. One should exploit such possibilities if the situation so demands. Perhaps the improved voice is due to tailoring in the dose distribution (figure 12) compared to that of the well-known Finzi-Harmer technique (1928) or to that of the external radiotherapy, used in a conventional technique.

Figure 12
Ellis' technique of brachy-therapy in laryngeal carcinoma with tailored dose distribution.



From Ellis F. (1975) Brachytherapy: with kind permission

PART II

THE MATERIAL & THE METHODS

THE RESULTS & THE COMMENTS

6 MATERIAL AND METHOD

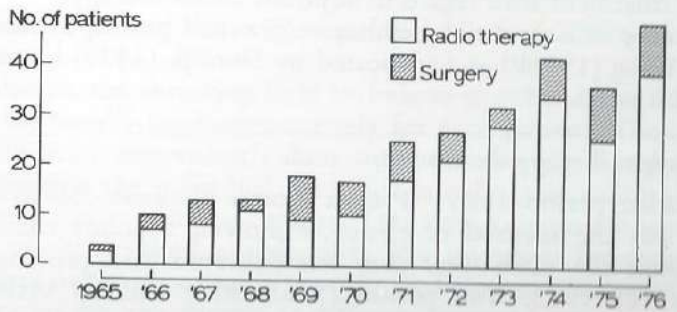
6.1 The patient material

One hundred and fifty consecutive patients with carcinoma of the larynx, treated primarily by radiotherapy since 1965 through 1974 in the department of radiotherapy of the Academic Hospital of the Free University are included in this study. In fig. 13 yearly distribution of a total number of 203 cases in relation to the applied primary treatment during this period is shown. A conservative treatment policy is reflected in this figure.
This Academic Hospital was constructed in early sixties and opened its doors to the public in November, 1964. This accounts for the small number of cases in the early years. Over the years the number of patients referred to the department of Otolaryngology has risen gradually and till the end of 1976 (fig. 13) a total number of 289 patients with laryngeal carcinoma has been treated in this hospital (AZVU).

6.1.1 The parameters

The study is prospective since 1974; the data of the patient material from 1965 through 1973 are collected retrospectively. The extent of the disease is re-classified according to the 1972 TNM classification wherever necessary. Clinical, endoscopic, histological and follow-up records are available for all. Pre-treatment radiological evaluations, an essential part of the TNM classification, are available in 85% of cases from 1965 through 1973. All patients treated in 1974 have had radiological assessments. Details of the treatment are well-recorded with at least one treatment check film available for each patient. All surviving patients have been personally examined by the author.

Figure 13
Yearly distribution of patients with laryngeal carcinoma in relation to the primary treatment methods (1965 - 1976).



6.2 Policy of treatment

The system of reference and the policy of treatment between the department of Otorhinolaryngology and the department of Radiotherapy in the Academic Hospital of the Free University (AZVU) have in general remained virtually the same over the last decade. The policy is conservative in favour of radiotherapy. All early cancers, TIS or carcinoma in situ, T1 and T2, are promptly referred for radiotherapy after histological diagnosis.
In recent years, a few supraglottic cancers have been treated by horizontal supraglottic laryngectomy with or without post-operative radiotherapy. Relatively small T3 and T4 lesions are also referred for radical radiotherapy, particularly if there are strong reasons for conservation e.g. psychological attitude and/or young age of the patients, patients with contra-indications for surgery etc.. Small nodal disease is not thought to be a contra-indication for radiotherapy as long as they are included easily in the fields of radiation.

The primary objective being the retention of the larynx, utmost attention is given to the primary tumor (T) during the radiation treatment. The nodal masses are given secondary importance but usually are covered within the initial field if possible. The treatment of nodal masses by radiation, in general, is thought to be less efficient and therefore is not to interfere with the high dose radiation therapy of the primary tumor. Such a conservative policy is justified when a rigid follow-up scheme is adhered to. The nodal areas are frequently and carefully watched constantly keeping in mind the possibility of development of nodal disease and surgery.
Patients with gross or massive T3 or T4 cancers are usually treated primarily by surgery, certainly so when associated with nodal disease. High dose post-operative radiotherapy is used when there is any doubt on the surgical clearance or nodal capsule infiltration by tumor cell. In recent years more attention is being paid to lymph or blood vascular tumor emboli as studied in the surgical specimen to formulate a better policy of treatment with regard to adjuvant chemotherapy.
Radiotherapy in a sandwich technique (pre- and post-operatively) as is used by Wang (1976P) and advocated by Hordijk (1977) has not been used in this series.

6.3 Radiation therapy details

In the earlier period 1965 - 1969 a shorter intensive course of radiotherapy was the method of choice. Following a policy change since 1970, about the same total dose was delivered with prolonged fractionation till 1973. The period (1965-1973) utilized orthovoltage radiation.
A 4 MeV linear accelerator has been in use since the end of 1973 and higher dosage has been practised.

6.3.1 Past radiation treatment, technique and dose

Radiations in most cases (1965-1973) were delivered via opposing lateral small orthovoltage fields, the usual size for glottic cancers being 4 x 6 cm^2, with 50 cm F.S.D., 250 KV., Thoraeus filter with bolus bags for the inhomogeneity of contour. When necessary (e.g. large glottic or supraglottic tumors with nodal mass) a larger applicator was used with resultant field size up to 6 x 8 cm^2 or rarely 8 x 10 cm^2. Check films were always taken with the treating unit. Rarely oblique fields were used particularly to direct the beam to the subglottic tumors with probable lower cervical, paratracheal or upper mediastinal nodes. The oblique fields were also used in patients with large nodal metastases to avoid high dose to the spinal cord.

In the earlier periods of this study (1965-1969) a short course of radiotherapy, usually 5400 R or more in 20 fractions in 4 weeks was used with an N.S.D. dose of 1950 to 2200 rets. From 1970, a protracted fractionation scheme has been followed with little higher total dose: 5400 to 5600 R or more in 30 fractions in 6 weeks. Because of the prolonged period, more gaps or intervals have crept up in this period. The volume has remained exactly similar and the N.S.D. has come down to 1750 - 1850 rets.

During the period (1965-1973), higher dose for larger tumor mass has not been practised. Neither was the field size varied to deliver a higher dose to a smaller volume (the shrinking field technique), after certain dose-levels. This was practised during 1974 with a 4 MeV linear accelerator.

6.3.2 Present radiation technique and dose: The shrinking field

The present technique utilizes supervoltage radiations with moderate field sizes which in rare occasions are increased if nodal mass has to be covered particularly in less differentiated supraglottic lesions. Iso-centric lateral portals are used with wedge filters. Individual shell masks with cut-outs are used for the fixation of the head and neck area.

Both fields are treated daily. The total daily dose of 200 rads is strictly adhered to.
Almost always, the shrinking field technique is utilized and 2 or 3 sets of fields are usually used consecutively for each patient. The changing of the field size is conveniently done with an iso-centric set-up and with this anticipation the individual patient is initially planned on the simulator. Rarely the iso-center is changed if the tumor regression is eccentric contrary to the previous anticipation. The iso-center for each patient with tumors of the same region is positioned almost at a similar site but the site varies for the tumors at different regions (e.g. supraglottic or subglottic areas). In all cases, the thyroid cartilage is within the field.

6.3.3 The field sizes and the dose

Moderate field sizes 5 x 5 to 7 x 7 cm^2 (rarely larger) are usually utilized initially depending on the mass of the tumor, the smaller field size being used for the small T1 lesion. For such lesions the fields are usually shrunk to 4 x 4 cm^2 at 5600 rads and a total dose of 6600 rads (± 1875 rets) is not usually exceeded.

For a T2 lesion, the field size is dependent on the size of the lesion. If a 7 x 7 cm^2 field size has to be used initially, two changes are brought in with 5 x 5 cm^2 at 5600 rads and 4 x 4 cm^2 at 6400 rads level. A minimum total dose of 6800 rads (± 1900 rets) is delivered to a small tumor and a maximum of 7200 rads (± 1970 rets) is usually not exceeded for a larger tumor or for a small tumor with impaired mobility of a cord. For the T3 or T4 tumors, a larger field size may initially be used and apart from the changes mentioned on the T2 tumors, a small 4 x 4 cm^2 or 3 x 3 cm^2 field is frequently used on the site of the remnants of the regressing tumor after 7000 or 7200 rads to raise the dose up to a maximum of 7600 rads (± 2050 rets).

The timing of the changes in the field sizes and the total dose is individually judged. The mass of the initial tumor, movement of the cord, speed of the tumor regression or response, radiation mucositis, age and general condition of the patient, presence of diabetes, arteriosclerotic diseases, inhomogeneity in the computerized iso-dose distribution are always considered carefully before a final decision is made. In aged patients, particularly with diabetes and vascular sclerosis, a dose of 7200 rads (± 1970 rets) is usually not exceeded.

The patient is examined by indirect laryngoscopy at least once weekly by the radiotherapist in the earlier period and more frequently during the last 2 weeks. At 7000 rads or above, the patient is examined almost daily.

Confluent mucositis is avoided but patchy mucositis over the tumor bearing area is frequently seen over the last few days of radiation treatment.

6.3.4 The dose distribution

The homogeneity of the dose distribution is considered to be one most important factor in reducing the complications. Accurate dose distribution is checked by a dedicated PDP 11/45 computer and more recently also by a Philips' Treatment Planning System Computer. More than 5% inhomogeneity is usually avoided. Considerable time and energy is needed to obtain the dose distributions of an individual patient treated by the shrinking field technique (fig. 14) particularly when one intends to keep the inhomogeneity below 5% level in the volume of maximum interest.

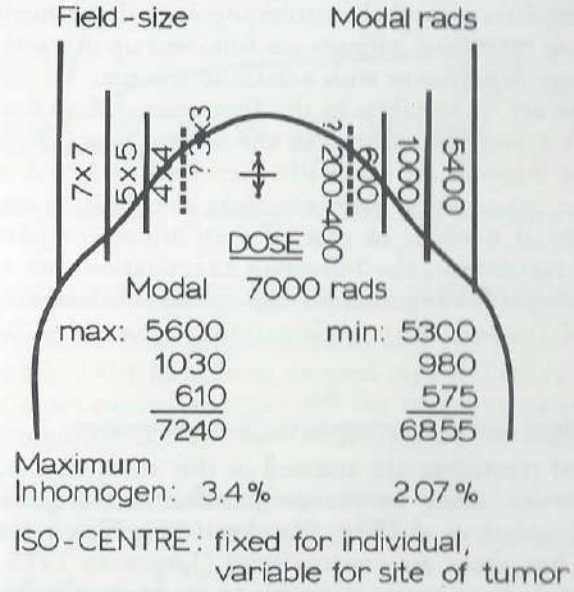
Treatments to each field are delivered 5 days a week. Small gaps or intervals of up to 5 days are usually not compensated by a high dose but

if the treatment is interrupted for more than a week, a higher dose is delivered to keep to the desired level of the ret dose.

Figure 14

Shrinking field technique: Computerized dose distribution:

For a modal dose of 7000 rads, the inhomogeneity in the volume of maximum interest is less than 5% when 3 field sizes are used. The smallest field 3 x 3 cm^2 or 4 x 3 cm^2 may be used to deliver a maximum dose of 7600 rads, when necessary. In this particular patient the homogeneity is less than ± 3,5%.



6.4 The N.S.D. ret calculations

The N.S.D. dose in rets is obtained by the formula following Ellis:

$$\text{N.S.D. in rets} = TD \times N^{-.24} \times T^{-0.11}$$

where TD is the total dose in rads delivered by a cobalt ^{60} (or a Linear Accelerator) unit in N fractions in T elapsed days.

The concept of elapsed days has been reviewed by Ellis (1974) recently but he considers (1976P) that this is of minor influence in a protracted fractionation scheme. Roentgen to rad conversion factor is taken to be 0.96 and R.B.E. factor of 4 MeV. photon has been accepted to be 0.85 for this study. Thus the total dose in 'R' (Roentgen) delivered by orthovoltage radiation has been converted to ret dose by the following formula:

$$\text{N.S.D. in rets for the orthovoltage radiations} = \left[\text{Total dose in R} \times 0.96 \times 0.85^{-1}\right] \times N^{-0.24} \times T^{-0.11}$$

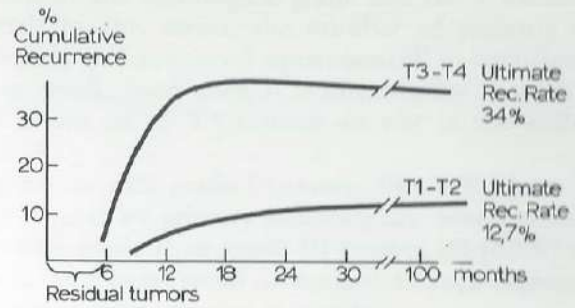
6.5 The follow-up

All patients are closely followed up. Initial few visits are arranged in both the radiotherapy and the otolaryngology departments. Gradually, with subsiding reactions, patients are followed up in a joint clinic in the otolaryngology department with a definite scheme.
Examinations are undertaken in the first year at 4 to 6 weeks' interval and at about 2 months' interval in the second year. During the 3rd to 5th year, the intervals are gradually increased to 3 to 6 months. From the sixth year, once-a-year visits are organised. Patients are encouraged to visit earlier if needed. In case of even minor complications or any suspicion of recurrence, the follow-up examinations are repeated more frequently. Direct laryngoscopies are arranged whenever needed. The frequency of the follow-up examinations is geared by the need of the patients.

6.6 The residues and the recurrences: Time sequence

The results of treatment are assessed in this study in a relatively short follow-up period. Most writers assume that late recurrences are new primaries (Kogelnik et al 1975, Fletcher 1973, Fletcher 1976P, Morrison 1974P) but there are controversies (Jørgensen 1975, Ellis 1975P) on this point. It is of course desirable to study the results with a longer follow-up. It is well-known, however, that the failures of radiotherapy are mostly the residual growths, evident right from the end of the therapy (Moss et al 1973, Morrison 1975P, Suit et al 1967, 1974). The remaining true recurrences in the great majority appear during the first 2 years (Suit et al 1967, 1976P, Jørgensen et al 1975) and practically all the advanced growths (T3, T4) that recur, do so within the first 12 months (figure 15). Less than 2% recurrence is observed by Suit et al (1967) after 24 months and about 1% yearly recurrence is noticed by Jørgensen (1975) after 5 years. It is also noticed by Ballantyne et al (1974) that recurrence is suspected in many instances months before the histological proof may be obtained.
Therefore a patient may be assumed to be locally controlled of the disease when he reveals neither residual/recurrent disease in the larynx, nor is there any evidence of suspect disease, 24 months following radiotherapy. With these rigid criteria the probability of the long-term local control rate for all primary laryngeal tumors is expected to be reflected in the short follow-up period of 24 months.

Figure 15. Recurrence in larynx carcinoma
Recurrence time & rate following radiotherapy in laryngeal carcinoma.



Modified from Suit et al (1967): Radiology 88, with kind permission

6.7 Computerized data handling: Retrospective and Prospective

The total material has been subjected to a computer protocol checklist. Patients treated in 1974 have been entered into the study-protocol by the author in a prospective manner. All the surviving patients, treated from 1965 through 1973, have been examined by the author personally.
For non-surviving patients during the above period, the information has been collected and entered retrospectively.

6.7.1 Data retrieval system

Sophisticated, efficient and accurate analysis of complex clinical data has been made possible with the development of a computerized data retrieval system during this study. The methodology and the experiences on this topic are being described in a series of articles (Hasman et al 1976, 1977, Karim et al 1977).

7 RESULTS

7.1 Number of patients: Regions

There are 150 patients in this study, 10 of them are females. In 119 instances, glottic area with or without extensions is involved. There are 25 supraglottic and 6 subglottic tumors in the series.

7.2 T classification and the histological grade

Table XII reveals the histological grade and the T classification of the total material. In this series, the number of patients with grade III tumor i.e. poorly differentiated squamous cell or undifferentiated carcinoma is very small. Even then it is noteworthy that 10 out of 14 T4 tumors and 5 out of 15 T3 tumors are not in the well-differentiated (grade I) group.
Of the 94 patients with grade I tumors, 74 (78%) have had local control of their tumors by primary radiotherapy, whereas of the remaining 51 patients with grade II or grade III tumors, 31 (60%) could be locally controlled. The same trend is noticed in each regional distribution but each group becomes smaller in number.

Table XII
Laryngeal carcinoma
T classification and histological grade (U.I.C.C. 1972)

	Grade and differentiation				
	Well I	Moderate II	Poor III	Not recorded	Total
TIS	8	0	0	0	8
T1a	24	10	0	1	35
T1b	6	2	0	1	9
T2	43	22	2	2	69
T3	9	4	1	1	15
T4	4	10	0	0	14
	94	48	3	5	150

7.3. Age

The range of the ages of the patients along with the mean and the median has been tabulated to reveal a gradient if any in the different T staging (Table XIII, fig. 16) of the total material. It is evident that such a gradient exists in this series. This has been done particularly to confirm the commonly held viewpoint that the pre-invasive tumors are found in a younger age group. From the mean ages of this small number of patients it is perhaps possible to imagine that the malignant proliferative processes may, in general, be a part of one progressive event and

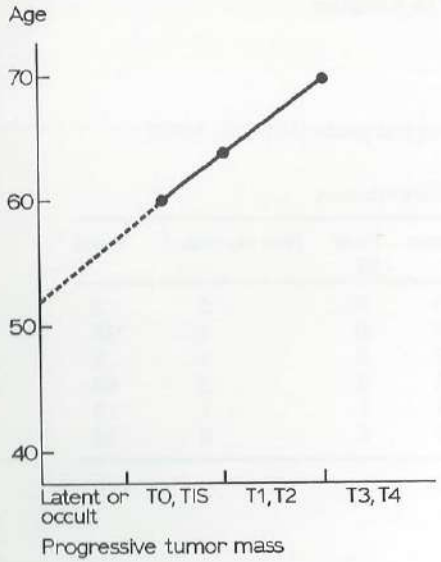
with time may eventually mature to become the most advanced disease of the laryngeal epithelium.

Table XIII

Age and the extent of the primary (T) in Laryngeal Carcinoma

	Age in years		
	Mean	age range	median
TIS	59	52 - 64	61
T1 and T2	63	37 - 85	58
T3 and T4	69	35 - 86	67

Figure 16
Mean age and tumor mass (T of TNM)



7.4 Sex

There are only 10 females as opposed to 140 males in this series. But only 1 female had recurrent disease (treated by a low dose of 1748 rets for a transglottic T2 tumor). Another is still in the suspect group with gradually subsiding laryngeal edema over the last 18 months. She was treated by 1890 rets for a T4NO supraglottic tumor. This result is much superior to that in males but consistent with the world literature (Table XI, chapter 3.1).

The N.S.D. dose range for these female patients is 1748 to 2010 rets with a mean and median of 1867 and 1889 rets respectively. Two developed arytenoid edema. One of the two, an obese lady treated by orthovoltage radiations, underwent tracheostomy for edema and had small areas of spontaneously healing skin necrosis. She is now alive and well with the closure of the tracheostomy. The other female, now reversing her suspect status, has already been mentioned.
The histological grade of the tumors in both sexes is noted in table XIV. The relative preponderance of grade II tumor in female is noteworthy although this could not influence the prognosis in females.

Table XIV

Sex and histological grade

	Grade I	II	III	Not recorded	Total
Male	89	44	3	4	140
Female	5	4	0	1	10
	94	48	3	5	150

T & N staging in females:

Out of 10, 1 female had TIS, 1 had T1, 6 had T2 and the remaining two had T3 and T4 tumors. Two had nodal disease as well. None presented with distant metastasis nor developed the same.

7.5 TNM classification

The total patient material, except 6 subglottic tumors, is classified according to the U.I.C.C. 1972 classification, as in table XV and XVI for the glottic and the supraglottic regions.

Table XV

Glottic Cancers: Local and regional disease status (T and N)

	TIS	T1	T2	T3	T4	Total
NO	8	38 a=30 b=8	48	8	4	106
N1a		2	4	1		7
N1b			1	1		2
N2a		1				1
N2b			2			2
N3				1		1
Total	8	41 a=30 b=11	55	11	4	119

Table XVI

Supraglottic Cancers: Local and regional disease status (T and N)

	T1	T2	T3	T4	Total
NO	3 a=2 b=1	4	4	2	13
N1a					
N1b		1		1	2
N2a		3		2	5
N2b					
N3		1		4	5
Total	3	9	4	9	25

Distant metastasis (M1)

Only 2 patients (T3 N3 M1 glottic and T4 N2 M1 supraglottic) had distant metastases at diagnosis. But 5 cases were suspects from the beginning of treatment and all of them developed florid metastases within a short period. Only one of these 5 cases was of glottic origin with a T4 NO tumor but the remaining were supraglottic in origin. Two cases were epilaryngeal T4 N2, 1 case had T3 NO and the other had T2 NO tumor of the lower supraglottic area.

7.6. Results with primary radiotherapy and salvage surgery

Primary radiotherapy has controlled the tumor locally in 107 out of 150 patients. Of the remaining 43 patients, 7 have presented with distant metastases. The ultimate fate of the 43 patients is presented in table XVII. The outlined treatment policy (6.2) in this study has resulted in preservation of voice in 71% of all the patients (actuarial data).

7.6.1 The advanced disease

17 Patients had completely fixed vocal cords. Eleven (64%) of them had local failures. However, the mean N.S.D. for this failure group is 1819 rets. Although speculative, one may hope to improve these results with higher dosage and uniformly better quality of radiations. Certainly the dose appears to be on the low side and the patients were treated with mixed modalities of radiations over a decade.

Table XVII

Ultimate Local Control (actuarial)
after
Treatment of residual/recurrent/metastatic disease following radiotherapy

	Radical	Palliative		
Surgery	27	1		
Surgery and Radiotherapy	4			
Chemotherapy		1		
	31	2	=	33
No treatment including wait & watch policy				10

Rate of salvage for radiotherapy failures : $\frac{28}{31}$ = 90%

Overall control rate for the failure group (including palliation) : $\frac{28}{43}$ = 65%

Ultimate local control rate

Radiotherapy	107	71%	
			= 90%
Salvage surgery	28		

For 29 advanced (T3 and T4) glottic and supraglottic tumors:

13 NED locally after primary radiotherapy = 45%
6 eventually salvaged by surgery

19 ultimately controlled = 66%

Out of 29 T3 and T4 tumors, 13 (45%) were controlled locally by primary radiotherapy and 6 out of 13 were eventually controlled after salvage surgery. Thus the ultimate local control (table XVII) rate for this selected, advanced group of tumors is 66% with salvage surgery and primary radiotherapy. This is comparable to the results reported in the world literature (tables VIII and IX, chapter 1), by two well-known workers in the field (Lederman 1965 and Bryce 1972).

7.7 Local failures: Analysis of causes

The assessable or assumed causes of local failures have been analysed in table XVIII. For this purpose, doses below 6000 rads (1770 rets) are considered inadequate, while tumors not responding to doses above 6800 rads (1900 rets) are taken to be radio-resistant. Each patient had at least one radiologic checkfilm available for examination in retrospect,

particularly to assess the geographic miss or localisation errors. It is clear from this table that there is a group of tumors which does not regress even with high doses of radiations. The majority of radiotherapy failures are evidenced as residues right from the end of radiotherapy. In this study 23 out of 43 patients appear to be in that category. Similar information is also recorded in literature (Suit et al 1967, Morrison 1975P, Ellis 1976P). The effect of higher dose in this group may be the subject of a future study.

Table XVIII

Assumed causes of local or regional failures

Geographic miss or inadequate volume of treatment	2
Gross underdosage	9
Nodal metastases (4 marginal, 1 outside field)	5
Radioresistant	23
Combination of above	4
	43

7.8 Causes of death

Forty patients of this series are already dead and the causes of death are enlisted in table XIX. One may note that almost 1 in 10 patients surviving laryngeal carcinoma may develop bronchogenic carcinoma. This high figure is well substantiated by Williams et al (1976) and may be expected from the point of view of existence of similar carcinogenic stimuli for the whole respiratory epithelium. In the series from Williams et al (1976), 43% of all deaths was due to bronchogenic carcinoma. In the present series, 33% of the deaths appear to be due to bronchus carcinoma. This may increase with a prolonged follow-up.

Table XIX

Causes of death in 40 patients

Unrelated to cancer			14
Related to cancer			26
A. New Primary			
Ca bronchus	9		
Ca bronchus and colon ca	1	:	10
Ca bronchus; definite separation from metastatic process difficult		:	3
Prostate carcinoma			1
B. Larynx carcinoma		:	12*

* some developed distant metastasis or had same at diagnosis

8 COMPLICATIONS AND SEQUELAE

8.1 Megavoltage versus orthovoltage radiations

No one would these days recommend orthovoltage radiotherapy in preference to higher quality radiations, even though there is evidence that control rates may not differ much (Suit et al 1974) in early laryngeal cancers. In this series, 108 patients were treated by the conventional units as opposed to 42 patients by a 4 MeV linear accelerator. Of the evaluable cases, a comparison is made between these groups of patients with regard to the late complications (table XX).

Table XX

Late complications following Radiotherapy

	Orthovoltage (108 patients) %	Megavoltage (42 patients) %
Skin patches of Hypopigmentation or Hyperpigmentation	67	3
Chondritis or Perichondritis	14	3
Atrophy or distortion of epiglottis or other areas	27	3
Telengiectasis of skin	48	
mucosa	30	0
both	15	
Transient edema	33	24
Persistent late edema (without recurrence) *	10	9
Necrosis (skin 3, cartilage 1)	3,5	0

* all degrees

It is evident that there is significant benefit from the supervoltage radiotherapy. However it may be noted that the 2 groups are not strictly comparable with reference to the extent of the primary tumor (T) or the histology and relatively more advanced cases with virulent histology have been treated by the supervoltage unit (table XXI and XXII).

Table XXI

T classification and
Percentage of patients treated by differing quality of Radiations

	Orthovoltage %	Megavoltage %
T1	37	27
T2	47	43
T3	11	6
T4	5	24
	100%	100%

Table XXII

Histological grade and proportion of patients treated by differing quality of radiations.

	Grade I %	Grade II %	Grade III %	Not recorded %
Orthovoltage	65	29	2	4
Megavoltage	51	49		

8.2 The edema, the necrosis and the ret dose

Necrosis is not seen in patients treated by megavoltage radiotherapy but is seen in 4 patients treated by orthovoltage units. Three of these patients were obese with short necks requiring high daily skin dose to deliver the same tumor dose. Except for one patient, who needed laryngectomy with reconstructive plastic surgery for gross cartilage necrosis, all healed with conservative care as the area of necrosis was limited only to the skin and subcutaneous tissue.

Persistent late edema in this series has been defined as follows: any degree of edema noticed 4 months after the end of the radiation that does not show evidence of prompt regression with conservative treatment e.g. abstention from smoking, voice rest with or without antibiotics and/or steroids. In general, a biopsy has been taken if the edema has been severe and persistent. Once biopsy is positive, the status of the patient is recorded as recurrent or residual and the computer rejects the diagnosis of edema. The patients treated by orthovoltage units revealing edema have been delivered doses ranging from 1762 to 2003 rets with a mean of 1891 rets. In the megavoltage group of patients the range is 1890 to 2040 and the mean is 1975 rets. Almost all patients with true edema have recovered after a variable period of suffering mostly from 4 to 9 months.

9 VOICE AFTER RADIOTHERAPY

The voice is assessed basically by a subjective scoring method. The scoring system considers a patient's own assessment, but attaches more significance to that of his wife and/or the clinician. The results are shown in table XXIII.

Table XXIII

Voice after Radiotherapy in evaluable cases

Better than pre-disease state	3	
? chronic changes / proliferative disease for years		(76%)
Normal or near normal	81	
Reasonable	11	(10%)
Unsatisfactory	15	(14%)

As mentioned in the previous review of the literature, all ranges, including improvement of voice better than the pre-disease state are recorded. Perhaps these patients had long term proliferative changes.

9.1 Post-therapy smoking habit and voice

The voice has been investigated in relation to the present smoking habit of the patients in table XXIV. It appears that the quality of the voice is significantly better in non-smokers or moderate smokers than in persistent excessive smokers.

Table XXIV

Post-treatment smoking habits and the quality of the voice

	Number of patients with present smoking habits			
Quality of voice	Non	Moderate	Excessive	Total
Good + Reasonable	30	45	20	95
Unsatisfactory	2	5	8	15
	32	50	28	110

$P < 0.05$ for each subgroup by statistical test for independence (de Jonge, 1963)

10 RESULTS ON DOSE RESPONSE

10.1 Results in relation to dose-response, failure and T-classification

There is an indication of dose-response for all laryngeal tumors in this series (figure 17). It is easily conceivable that this is the upper part of the sigmoid dose-response curve and with higher doses above 2100 rets perhaps little benefit may be anticipated.

Figure 17.

Dose response in 150 patients with larynx carcinoma

Indicator curve to reveal dose response in the overall patient material. Different dose points used for the different groups of patients have been joined to indicate the slope of the dose response curve.

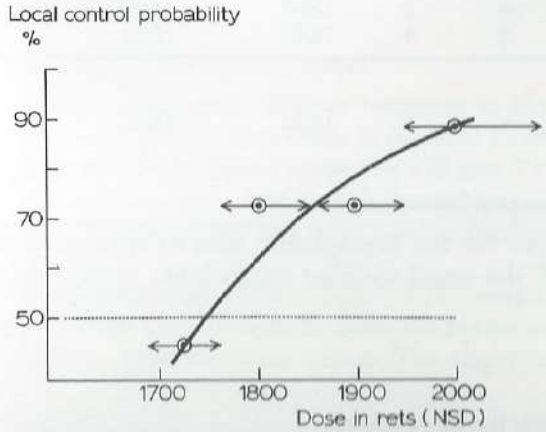


Table XXV shows the group of patients in relation to the regional T classification, ret dose and local failures. Apart from TIS and T1 lesions, it appears that the mean dose delivered to patients with local control is higher than that delivered to patients who developed local recurrences.

TABLE XXV

Larynx Carcinoma
Dosage Analysis (in rets): T Classification

Tumor Region Classification	Total No. Patient	Local Failure	Mean NSD in rets for Failures	Mean NSD for Successful Cases	Local Failures Rate
Glottic					
TIS + T1a + T1b	49	4	1930	1850	8%
T2	55	17	1760	1850	31%
T3	11	7	1870	2000	63%
T4	4	3	1780	2010	75%
Supraglottic					
T1	3	0		1920	0%
T2	9	4	1850	1870	45%
T3	4	2	1850	1890	50%
T4	9	4	1840	1870	45%
Subglottic					
T1 - T4	6	3	1690	1880	50%

10.2 Dose response in supraglottic tumors

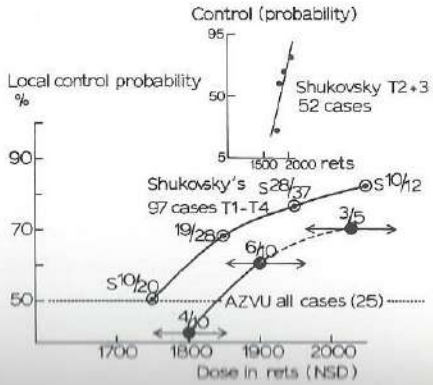
The dose response curve for the supraglottic tumors appears to be rather steep. Because of the small number of patients in this group, a curve is plotted from Shukovsky's (1970) data for all supraglottic tumors of his series to compare the slope of the curve of this (figure 18) series with that of his.

It appears that both the dose response curves for total patient material in supraglottic areas have similar slopes. Morrison's data are indicative of a similar slope (1962, 1975). From the small patient material of this series, it is not desirable to subdivide the supraglottic tumors. Further patient material shall be needed for detailed analysis. However, Shukovsky's steep dose response curve as is originally drawn, is presented in the offset (figure 18) for comparison.

At higher doses, the present material includes only few patients.

Figure 18
Dose response in supraglottic larynx carcinoma

Comparison between Shukovsky's data and data from the present series. It is emphasized that the number of patients with supraglottic tumors is small in this series. Even then, the slope of the curve indicates presence of steep response as is evidenced in the literature (2.3).



10.3 Dose response in subglottic carcinoma

No dose response curve is attempted as there are only 6 patients in this subgroup. However table XXV (10.1) suggests a tendency towards response at higher dose.

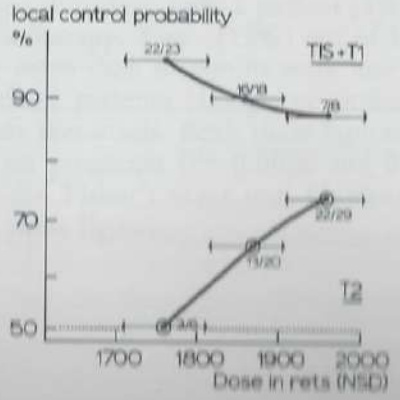
10.4 Dose response in glottic carcinoma

There is an overall indication of dose response in this group of glottic tumors. Table XXV (10.1) shows this in relation to the T classification, ret dose and local failure. Apart from the TIS and T1 lesions, the mean dose delivered appears to be higher for the patients with local control of T2, T3 and T4 tumor than the dose used in patients with residual or recurrent disease.

Tumors with smallest mass (TIS + T1a + T1b) reveal no dose (fig. 19) response at all while the T2 tumors indicate better control with higher dose with a steep dose response curve. The slight worsening in local

Figure 19
Dose response in early glottic carcinoma

49 TIS + T1 tumors with flat indicator curve with no dose response and 55 T2 tumors with a steep response.



response for the smallest tumors with increasing dose is difficult to explain but is also recorded by others (Horiot et al 1972 : 2.2 fig. 5).

Amongst 15 patients with advanced growths (T3 and T4), 5 (33%) are locally controlled by primary radiotherapy.
High doses above 1900 rets have been delivered to 5 patients with 3 local controls. Moderate doses between 1850 to 1900 rets have been received by 5 patients with 2 local controls and doses below 1850 rets have failed to control the advanced tumors in 5 patients.

10.5 Statistical evaluations

With Fisher's Exact Tests (Armitage 1970), the statistical significance of the differences in dose response is examined. In none of the figures the difference has reached statistical significance (95% confidence level).

11 OTHER FACTORS OF PROGNOSTIC IMPORTANCE

11.1 Duration of symptoms and prognosis

The duration of symptoms is analysed in relation to the local control following radiotherapy. For this purpose, a cut out is used at 6 months in relation to the duration of hoarseness. There are 20% recurrences or suspects out of 50 cases who had hoarseness of longer than 6 months duration. The local failure rate is 16% when the duration of hoarseness is less than 6 months. Thus, in this study, duration of symptoms has no correlation to local control. (The date of the first treatment has been considered as a basic parameter in this study).

Combination of symptoms and prognosis.
Pain in the ear when associated with hoarseness appears to be correlated to worse prognosis. There are 20 patients in this series with these two symptoms combined. Out of these 20, 7 had local failure of whom 5 had a fatal outcome. Only 2 cases out of 5 were salvaged by surgery.

11.2 Prognosis and interplay of multiple factors

Out of the 143 patients without distant metastasis, 80 had relatively grave chronic ailments and 63 had no associated diseases. Chronic respiratory diseases were recorded for 46 patients and cardiovascular diseases in 30 cases with 17 long-term anticoagulant users. Only 2 patients had a previous history of cancer. Two had history of diabetes. Twenty-five of the living patients revealed some sort of history of allergy e.g. skin-rashes on drug or food, hayfever, allergic rhinitis etc.
Of the living patients, 31 revealed a history of cancer in the family.
Interplay of multiple factors in the cure of cancer is one point of importance but not always practical to correlate.
Because of the computerization, it was possible to find out that out of the 80 patients who had some associated disease, 34% could not be locally controlled by radiotherapy. This figure may be contrasted with a local failure rate of 10% of the 63 patients with laryngeal carcinoma who had no associated diseases. Out of 25 cases who revealed some evidence of allergic disorders, only 1 patient (4%) could not be controlled locally by radiotherapy. Two (12%) out of 17 patients who used anticoagulants for more than 6 months were not controlled by radiotherapy. None of these patients (allergic or anticoagulant users) developed nodal or distant metastasis. Both these factors have significantly different influence on prognosis ($P = 0.0006$ and 0.0025 respectively) according to two sided Fisher's exact test. However there may be elements of selection in these figures.

Histological differentiation could be correlated to the prognosis in this study. But the number of patients is too small to be reported in detail for each region (7.2). Evidence of the presence of host defence mechanism as revealed by infiltration of the tumor by lymphocytes and plasma cells was recorded in 95 patients. In at least one patient, definite destruction of the tumor by such infiltrations was noted by the pathologist. In the remainder, these findings were unfortunately not recorded. Clinical significance of such infiltrations could not be elicited in this study.

However, if allergy in general is an expression of delayed hypersensitivity reactivity which may work in the field of dynamic host defence mechanism against tumor, it may be noticed that only one out of 25 (4%) allergic patients could not be locally controlled by radiotherapy. Similarly one may speculate that the associated diseases have significantly ($P < 0.05$) interplayed and inhibited the host defence mechanisms of 80 patients with associated diseases resulting in 34% local failure rate whereas the treatment failed locally only in 10% patients who had no associated diseases.

PART III

DISCUSSIONS

&

OPTIMUM DOSES

12 DISCUSSIONS

In general, this study appears to be of a representative series of patients with laryngeal cancer, treated by radiotherapy. In the previous chapters comments and some discussions have been put together with the results and therefore a conventional discussion is avoided here. However, the study has provided some information, not usually available in the literature. These points along with some other features of this study shall be further discussed.

12.1 Quality of radiations

These patients heve been treated with mixed modalities of radiations over a period of 10 years. While 5 years survival rate of patients with early laryngeal carcinoma does not appear to differ according to the quality of radiations (Suit et al 1974, Vermund 1970), it improves in patients with advanced tumors treated by megavoltage radiotherapy (Suit et al 1974). Hardly any literature is available on the local control of the tumor from the standpoint of treatment by differing qualities of radiation. Speculatively however, results of modern high quality radiation therapy with sophisticated techniques should be better than those in a group of patients treated by mixed modalities such as is reported in this series.

12.2 Sex

It appears that the contention of Lederman (3.2) to treat all female patients suffering from laryngeal carcinoma primarily by radiotherapy irrespective of staging is worth following. The contention appears to be well-substantiated by the small number of patients with worse histological grade in this series (7.4) and the available international data (table XI, 3.1).

12.3 T-classification, tumor volume and a practical modification of (T)

For the sake of clarity, (T) of the TNM system of classification has been in the limelight of this analysis as is conventional for such studies (Shukovsky 1970, Kok 1971, Wang 1974 etc.).
However the importance of the nodal disease is not denied but not undertaken for analysis because of the small number of patients with nodal disease.

Volume of the tumor mass

In this study, frequently the volume of the primary tumor mass has been referred to and emphasized. In radiotherapy, the tumor mass or the total number of cells is of great importance although not usually considered in day-to-day clinical practice. In general, a higher radiation dose is known to be necessary for larger tumor mass for greater cell kill.

The basic radiobiological principles, aptly explained schematically (fig. 20) by Barendsen (1977P), imply that the dose response curve may be flat for the smallest tumors. In this series, it appears to be true for such tumors namely TIS, T1a, T1b of the glottic region. It is easy to imagine that the glottic area being small, cannot harbour a tumor with larger tumor mass without extending to the other regions. The supraglottic region however, being extensive, may accommodate a much larger T1 tumor. The inadequate patient material in supraglottic group does not permit valid assessment on dose response in this study and therefore is avoided but speculatively dose response in this region may exist (Morrison 1962, Shukovsky 1970, Nematullah et al 1974) even for T1 tumors.

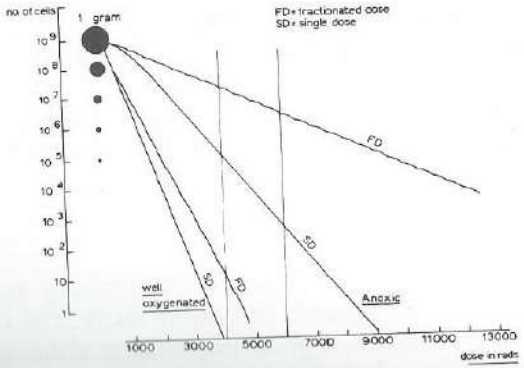
For the patients with T2 glottic tumors, the dose response curve (10.4; fig. 19) appears to be quite steep in this series. It has been emphasized (1.4) that the T2 glottic is a rather heterogeneous group in the recent TNM classifications and may comprise of small or large tumor masses with different behaviour and radiosensitivity (2.2).

Similarly in the more advanced laryngeal tumors, the biological behaviour of a tumor with a larger mass or varied patho-physiologic characters may be different and a homogeneous subgrouping may be advantageous for the dose response analysis in a future prospective study.

With this basic idea in view, a workable modified (T) classification (within the parameters of the U.I.C.C. TNM 1972), has been in use the department of radiotherapy (AZVU) since 1975 and is described here. Some schematic examples are also shown (fig. 21). The value of such modifications lies in the help rendered to the clinicians in assessing the volume of treatment and the maximum dose to be used in a particular patient. Whether there is any other practical advantage of the system, shall only be revealed by posterity.

Figure 20

Basic principles of radiobiology on tumor mass, oxygen, fractionation and dose



From Barendsen (1977P)

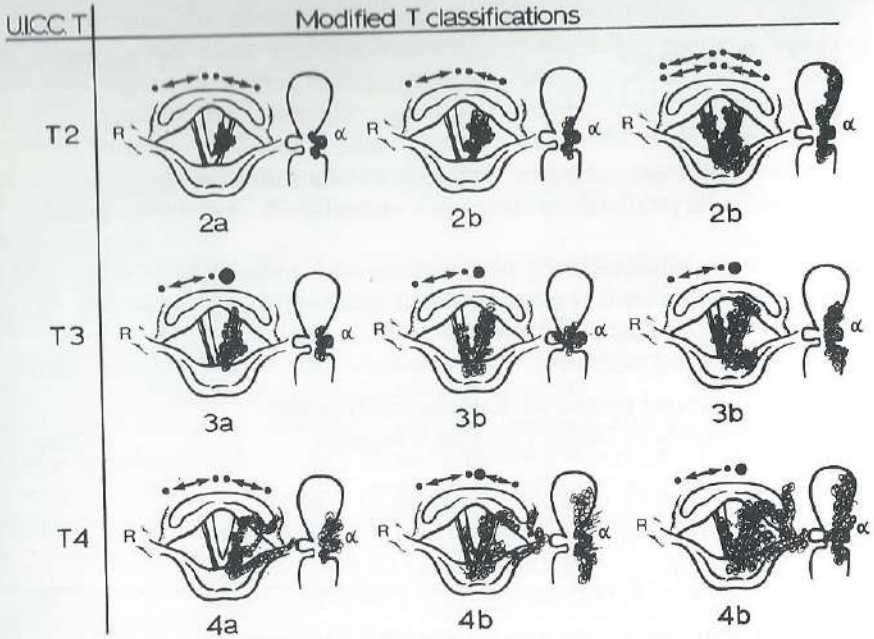
For smaller number of cell kill, the parallel curves will require lower dosage.

Modified Classification of the Primary (T) tumor

Modification (used in the Radiotherapy Dept. A.Z.V.U. with special emphasis on tumor mass) on U.I.C.C., 1972 classification of laryngeal carcinoma.

U.I.C.C.	Description	T modification
T1a	same as U.I.C.C.	T1a
T1b	same as U.I.C.C.	T1b
T2	Tumor extending to 2 regions in one side of the larynx without impaired mobility	T2a
	or Tumor limited to 1 or 2 regions with impaired mobility or 2 regions involved bilaterally or 3 regions involved with or without partially impaired mobility.	T2b
T3	Unilateral tumor with complete fixation of one cord limited to 1 or 2 regions	T3a
	or Tumor with complete fixation of cord or cords. extending bilaterally or to 3 regions or showing radiological evidence of deep invasion (ice-berg) before biopsy (e.g. piriform sinus).	T3b
T4	Tumor with minor extralaryngeal involvement e.g. medial wall of piriform fossa, valecula, postcricoid area, minor cartilage involvement with or without impaired movement of the cord	T4a
	or Massive tumor with gross involvement of the extralaryngeal structures or gross bilateral tumor with complete fixation but minor extralaryngeal extension	T4b

Figure 21
Some schematic illustrations of the modified (T) classification used in the radiotherapy dept. (AZVU).



12.4 Dose response controversy: A speculative hypothesis

An important question may be raised now on the controversies focussed on the main topic in this study. Why should one series reveal dose response in one limited group of tumor, say for example in glottic carcinoma (T1 or T2 or T3) and why would other authors fail to get such response in a similar group of tumors? This is a difficult question but one may try to consider the possibilities:

If the dose range is high and does not vary much, one basically remains in the upper flat part of the sigmoid dose response curve and therefore one may expect to obtain a flat response. This is reasonable and the literature (Fletcher 1964, 1970, 1974, Marks et al 1971, 1973) has already considered this possibility. The other possibility is more speculative and interplay of multiple factors may come in. The radiosensitivity of a group of tumors may depend on a host of factors:

- Tumor mass or total number of cells in a tumor and its biological character.
- Hypoxic foci e.g. necrosis, emboli, fibrosis etc..
- Cell kinectics e.g. proportion of cells in G0, G1, G2, S and M phase of clonogenic or non-clonogenic groups with shift possibilities.
- Host defence mechanism, tumor-angiogenetic factors along with micro-angiogenesis from fractionated radiotherapy, other biologic factors etc..

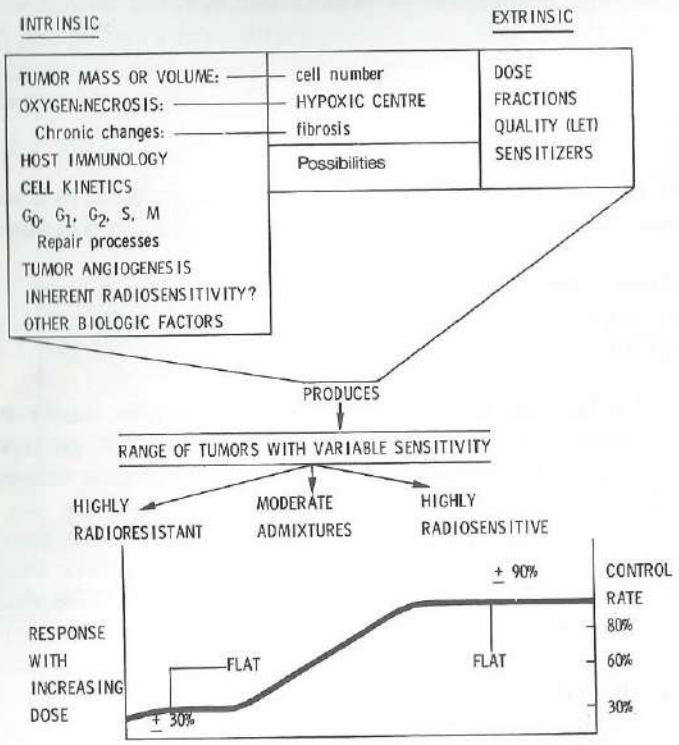
These factors may result in tumors of similar morphology, in a varying range of radiosensitivity. This may broadly be classified in 3 groups:

Highly radiosensitive
Moderately radiosensitive
Radioresistant

If this state of affairs actually exists clinically, one may easily notice that no dose response may be obtained in patients with greater preponderance of tumors of group 1 and group 3, whereas dose response is possible to obtain in tumors with moderate radiosensitivity (fig. 22). In clinical practice it is well-known that even a moderate dose has cured a few of even the advanced tumors completely (microscopic evidence is provided by de Jong 1975), whereas even e very high dose shall not control the local tumors of some patients (7.7). In our experience, in some patients with T3b and T4b tumors, a dose of 7600 rads (± 2050 rets) was delivered in seven and half weeks with shrinkage of the tumors but complete regression could either not be obtained or the tumor recurred within 12 months (Karim et al, 1977).

Eventually one may speculate that selection in this line does occur in some situations at least, resulting in possibilities of eliciting dose response in some tumors but not in others.

Figure 22
Radiosensitivity and dose response in a group of tumors



12.5 Evaluation procedures

One does not find many statistical evaluations in this study and this has been deliberate due to the nature of the work. Basically this is a clinical study, mostly with retrospective material in search of dose response in radiotherapy for carcinoma of the larynx. This is a precise topic but multiple factors interplay in every clinical set-up and therefore such factors have also been looked at in this study. The basic objective is also clinical: if dose response does not exist, then a reasonable dose should be chosen for a group of tumors, whereas if it does exist, we should orient our ideas about the total dose for a type of tumor and try to deliver a higher dose. Apparently it looks simple enough to avoid statistical calculations and to direct attention towards better patient care. However, one may ask: "How do you know you've done any better?" (Schneiderman 1975).

There starts the difficulty. The problem of comparisons with the past is well-known. Improved diagnostics, better technology and improvement in ancilarry care may silently creep inside the results to show false improvement with higher dose. Fortunately we may be almost certain that this was not the case in this series. Higher doses of the order of above 1950 rets were delivered before 1970 and around 1900 rets after 1973. Therefore a built-in protection against such biases is already available in the study. The questions of early diagnosis and improved ancillary care do not play important roles during the period in question (1965-1974).

The range of responses to radiotherapy is well-known, over the last few decades for groups of laryngeal tumors (e.g. T1, T2 etc.) and data obtained in this study appear to be representative. Therefore the variables may be assumed not to be varying too much.

In such a situation the 3 regions (glottic, supra- and sub-glottic) and 5 tumor sub-groups (TIS, T1, T2, T3, T4) have already subdivided the small patient material. Different dose ranges have further reduced the number of patients into still smaller sub-groups. It is unfair to expect statistical significance from such numbers. That is why perhaps, so far, almost all authors have not even attempted to work out the statistical significance of their data on dose response.

It is interesting to note that the only publication (Fayos 1975) with worked out statistical significance does find improvement in results in T1 glottic carcinoma with higher dose but no significant improvement in any other sub-group, even not in the supraglottic cancers. In the context of radiobiological principles, dose response in T1 glottic tumors may be doubted, whereas from historical perspective, non-availability of dose response in supraglottic cancer is rather contradictory as almost all authors do get dose response for similar tumors.

There may be well-justified valid reasons for such fallacies and perhaps more shall be known in future. For the present, this fallacy appears to speak out of unjustified confidence in statistically satisfying exercises. These data from Fayos (1975) are difficult to explain at present but may be analysed in future when more is known. Fayos (1975) himself is aware of the fallacy and it does appear to him that higher doses could have controlled more cases both in glottic and supraglottic tumors, particularly with advanced lesions. Perhaps such examples evoked Freireich (1976) to formulate and focus on "The good is bad and the bad is good" statistical dilemma.

It is repeated that the crux of the issue lies on the question of dose response and concrete statistical conclusions are not possible to draw from this study. However, with all the limitations, the study tends to reveal the presence of dose response.

12.6 The optimum dose range: a guide line

The local control rate for the true TIS and T1 carcinoma is high, as is evidenced in this series.

Greater number of cell kill is not required for a small number of tumor cells from the point of view of radiobiologic principles and therefore higher dose may be unnecessary for these tumors, unless the tumor may be harboured at a site where it may grow considerably without involving another region (e.g. a large supraglottic T1 tumor).

It is therefore considered that 33 fractions of 200 rads daily with a total dose of (± 1875 rets) 6600 rads may bring the optimum - the maximum control rate with virtually no complication for this group of tumors (TIS and T1). One may shrink the field of treatment to avoid complications. The T2 carcinomas may, on the other hand, consist of all sorts of tumors, small, medium or large with varying biological virulence, natural history and radiosensitivity. For the T2 tumors, therefore, the optimum dose may vary from 6800 rads in (± 1900 rets) 34 fractions up to 7200 rads in 36 fractions (± 1970 rets). The total dose may depend on the volume, radiation reactions, speed of regression of the tumor, degree of inhomogeneity in dose distribution etc.. It is preferable to shrink the field to focus on the residual mass to deliver a higher dose. Usually 6800 rads (1900 rets) are enough for a small tumor without impaired mobility of the cord whereas 7200 rads (± 1970 rets) are to be considered for tumors of small volume with restricted movement of the cord or for tumors with larger volume (T2b fig. 21).

For the advanced tumors a maximum tolerated dose, usually in the range of 7200 to 7600 rads (± 2050 rets) with tailoring and shrinking of the treatment volume is considered to be the optimum. At daily dose-rate of less than 200 rads an extra benefit may come out by cautious experimentation to reach higher dose levels, but we have not yet gained any experience on such extra-prolonged fractionation. All fields should be treated daily and a daily dose of 200 rads should not be exceeded. Inhomogeneity below 5% in the dose distribution may be helpful in reducing complications. Individual variations are always necessary.

Modern radiotherapy with sophisticated techniques should not impose any increased incidence of complications on modern surgery for laryngeal tumors and one should be watchful of the risks of complications when treating patients with increasing doses.

Knowledge, understanding, experience and skill both in modern surgery and radiotherapy may rescue us from the doubts on the risks of life-threatening complications and it may be possible to deliver high dose to give the patient 'the benefit of doubt of dose response' to preserve voice, at least in a selected group of advanced laryngeal carcinoma. The question of selection is a matter of joint attitude of the treatment team - the surgeon and the radiotherapist. It will always depend on the mutual respect, the mutual ability and the co-operations between these specialists. If they are alive to the team spirit and to the problem of an individual patient, the interest of the latter will be served best.

SUMMARY AND CONCLUSIONS

One hundred and fifty consecutive patients with laryngeal carcinoma treated primarily by radiotherapy in A.Z.V.U. from 1965 through 1974, have been studied with a computerized data retrieval system to reveal the dose response in relation to the local control of the primary tumor (T).

Literature on the subject (part I) is especially controversial on the question of dose response in glottic carcinoma. Virtually no such controversies exist in supraglottic epithelial malignancies. Almost nothing is known on the dose response of rare subglottic cancer. The response of the primary tumor (T) in relation to the increasing dose at the three regional subdivisions of the larynx with the parameters of the U.I.C.C. (1972) TNM classification is reviewed along with the nodal disease and other prognostic factors. The parameter (T) of the TNM system is focussed. This parameter does not appear to be beyond the scope of improvement. The female patients appear to be more radio-curable than the males.

In part II, the patient material of this study, the policy of treatment, the technique, the dose and the results are presented with relevant comments and discussions. The results of this series appear to be representative in the light of the published work. Evidence of overall dose response in glottic, supraglottic and subglottic carcinoma is indicated in this study. However, the number of patients in the latter two regions is small. Glottic carcinoma does not reveal dose response when the tumor is small (TIS and T1) but yields to higher dose in T2 group. Dose response is also indicated in a small number of patients with advanced (T3 and T4) carcinoma.

Other prognostic factors, complications and the voice of the treated patients are discussed. Only minor complications are encountered with cautious high doses of megavoltage radiations. The voice appears to be significantly worse with post-therapy excessive smoking.

In part III, the important and relatively less focussed aspects are discussed in further details to understand the controversies on dose response. A modified T classification is proposed to obtain homogeneous subgroups for further dose response studies. The optimum dose ranges for laryngeal carcinoma are defined with the objective of higher local control with minimum complications.

Multiple factors have been analysed in this study with the development of a computerized data handling system. In the appendix, one of the articles on the development of a system on Computerized Data Retrieval in clinical research in radiotherapy is reproduced.

SAMENVATTING EN CONCLUSIES

Deze studie betreft de gegevens van 150 opeenvolgende patienten met larynxcarcinoom van 1965 tot en met 1974, die in eerste instantie met radiotherapie werden behandeld. Met behulp van een computer werd een 'data-retrieval-system' gebruikt om klaarheid te brengen over de relatie tussen het effect van een bepaalde dosis (dose response) en de locale genezing van de primaire tumor (T).

De literatuur over dit onderwerp (deel I) is vooral wat betreft de glottiscarcinomen controversiëel. Bij de supraglottische carcinomen bestaan deze controversen feitelijk niet. Over de 'dose-response' bij zeldzame sub-glottische tumoren is vrijwel niets bekend.
Voor elk der drie delen van de larynx afzonderlijk wordt de 'dose response' beschouwd met de parameter (T) van de U.I.C.C. TNM-classificatie van 1972. Daarbij worden ook in aanmerking genomen de aanwezigheid van lymphkliermetastasen en andere prognostische factoren. Vooral de parameter T van het TNM systeem wordt in ogenschouw genomen. Deze lijkt nog wel voor verbetering vatbaar. Vrouwelijke patienten blijken beter radio-curabel te zijn dan mannen.

In deel II komen de bestudeerde patienten ter sprake, alsook de gedragswijze bij de behandeling, de techniek, de dosis en de resultaten. Gezien in het licht van de gegevens van de literatuur schijnen deze resultaten wel representatief te zijn.
Uit deze studie blijkt, dat 'dose response' bestaat bij de glottische, de supraglottische en de subglottische carcinomen. Het aantal patienten met deze laatste aandoeningen is echter gering. Bij het glottische carcinoom blijkt geen 'dose response' te bestaan als de tumor klein is (TIS en T1), maar deze bestaat wèl in de T2 groep. Er zijn ook aanwijzingen voor dose response in een klein aantal verder voortgeschreden tumoren (T3 en T4).
Andere prognostische factoren, complicaties en de kwaliteit van de stem van behandelde patienten worden besproken. De stem blijkt significant slechter te zijn bij overmatig roken na de therapie.

In deel III worden alleen de belangrijke en betrekkelijk weinig belichte aspecten nader besproken voor een beter begrip van de controversen aangaande 'dose response'.. Een gemodificeerde T classificatie wordt voorgesteld, ten einde meer homogene subgroepen te verkrijgen. De optimale doseringsschema's voor het larynxcarcinoom worden nader toegelicht. Het doel is: betere locale genezing en zodoende vermindering van de complicaties.
Met de ontwikkeling van een computerprogramma zijn in deze studie de vele factoren geanalyseerd. In de appendix is één van de reeds gepubliceerde artikelen over de ontwikkeling van computer 'data-retrieval-systems' opgenomen.

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(P indicates personal communication.
Most authors with 'P' have kindly allowed me to use their data.

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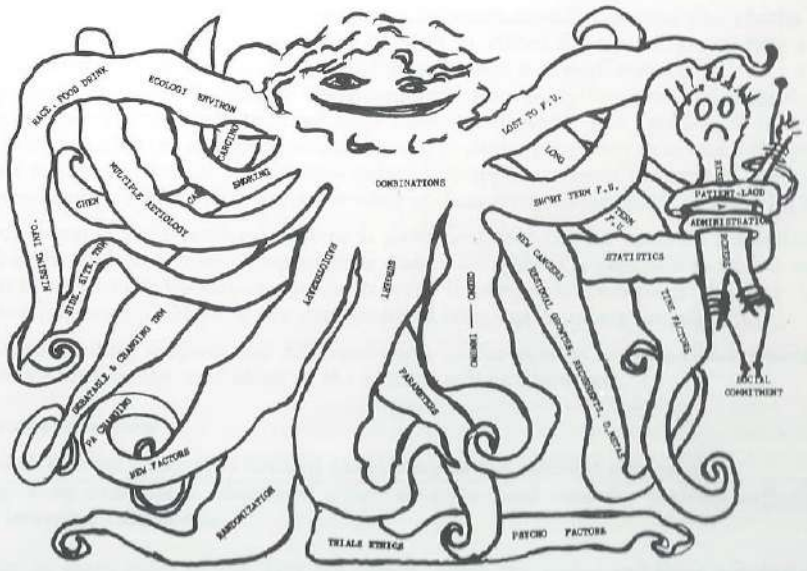
A DATA RETRIEVAL SYSTEM FOR CLINICAL RESEARCH IN RADIOTHERAPY

modified from: MEDINFO 77, ed. by D.B. Shires & H. Wolf, North Holland Pub. Co. Amsterdam, 395-300, 1977: (Proc. of the Second World Conference on Medical Informatics, Toronto, Aug., 1977.)

Improvement on existing treatment policies and methods is the main objective of clinical research. The complexities of such researches are known. Some are shown here:



Help from the computers may be advantageous in this field. Since 1974, an attempt was made to develop a data retrieval system with emphasis on clinical research. This system, which is still under development, is outlined here.

A DATA RETRIEVAL SYSTEM FOR CLINICAL RESEARCH IN RADIOTHERAPY

A data retrieval system is described that can be used interactively on a dedicated computer. The system is keyword oriented and can be used by non-computer experts for clinical research.

Most clinicians feel strongly for the need to continuously analyse the results of their treatment methods but few may be able to afford the time. Data storage and retrieval with a computer can then be of great help if it is performed efficiently and easily. Since the introduction of minicomputers possessing large mass-storage devices it has become possible to store large amounts of data. The problem is now to determine which data should be collected and to devise programs that make the process of retrieval efficient. Up till now only a few applications in the area of oncology have been published that use some kind of data retrieval language. ([1], [2], [3]).

In this paper a data retrieval system is described that can be used on a relatively small dedicated computer, coupled to a disk. The system is designed in such a way that it is easy to use by non-computer experts. It consists of two parts: the data description language (DDL) and the data retrieval language or query language (QL).

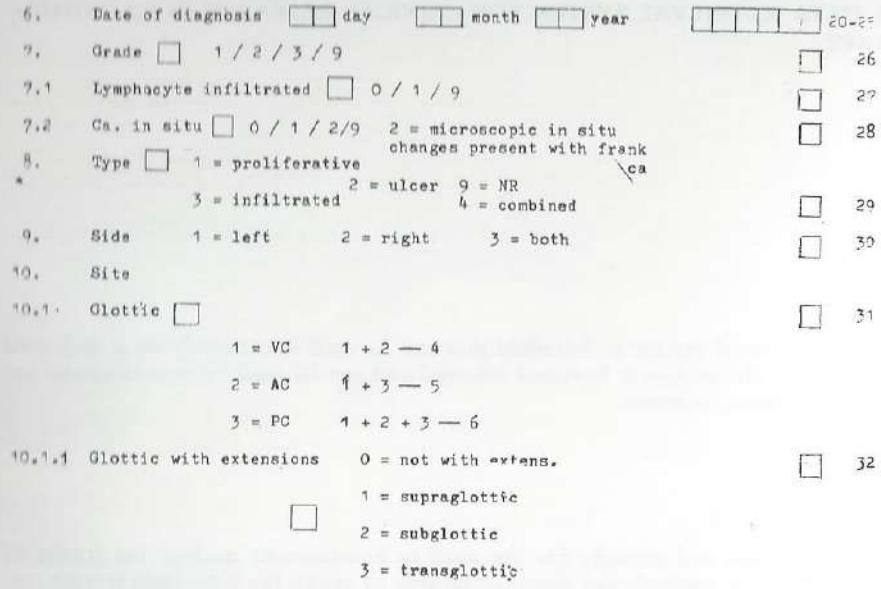
In the succeeding sections the different parts of the system are described, whereas in the last section the usefulness of the system will be discussed.

2. System overview

For each patient a record is defined containing all the relevant clinical data.
In fig. 1 an example is shown of a part of a protocol used for patients suffering from laryngeal carcinoma.

As can be seen, most of the data are coded. Since the codes and their translations appear on each protocol no codebook is necessary to translate an item into a number. In each case the data in the protocol are punched onto cards. The positions on the card where an item will be punched are displayed next to the squares that contain the data. Recently direct type-in system is developed.

Fig. 1
A part of a protocol check-list.



The punched cards are read into the computer and then stored on disk. The structure of the file is such that every record (the total information of one patient) can be directly accessed by the program. It is also possible to go from one patient to the other in a sequential way. To this end each record refers to the following record by a pointer.

To define the names of the different variables, their starting positions on the card and their lengths, a data definition language is necessary. Also the datatype (integer, real or floatingpoint), the allowed range of the variable and the symbolic description must be specified. The query language uses the above information to understand the questions that will be asked.

The system has been implemented on a PDP - 11/70 computer running under the RSX-11D operating system. The program has been designed in such a way that it can run in any computer having an operating system permitting overlay structures, a FORTRAN compiler, a disc storage device and some input/output medium. (A Teletype is always needed, a Mark-sense reader can be very useful [4]).

3. The data description language

The data description language (DDL) has been designed to make the insertion of data names and their attributes easier. The DDL uses four commands. When entering names for the first time the A(dd) command is used. This command expects the following input:

The item name, the first position in the record, the length, the data type, the minimum and maximum values that are allowed and the symbolic description. In fig. 2 an example of variable description is given. Among others the variable named sex is defined. It starts in position 6, its length is one position, the data type is integer, the minimum value is 1, the maximum value is 2. The symbolic description indicates that 1 stands for male and 2 for female. These symbolic descriptions can be used for query and output purposes. The Modify command is available to correct any mistyped attribute values whereas the Rename command makes it possible to change the name of a certain item. Items can be deleted by the delete command.

The variable names together with the attribute specifications are stored in a description table. The position in this table is stored in a pointer array. For a specific variable the index of the pointer array is obtained by hashing the variable name. Later on the variable description is directly accessible through this pointer array.

For each patient the data on the card are checked and an error message is given when the data do not obey the specifications.

Fig. 2
A system for using DDL.

```
COMMAND :
A /SEX/6,1,1,1,2 ( 1=MALE, 2=FEMALE)
COMMAND :
A /GRADE/20,1,1,1,9
COMMAND :
A /SUPRAGLOTTIC/34,1,1,1,2 ( 1=YES,2=NO)
COMMAND :
BYE
DO YOU WANT THE DICTIONARY LIST? TYPE Y(ES) OR N(O)
YES


S U M M A R Y  O F  T H E  D A T A D I C T I O N A R Y                PAGE   1
DATE 23-AUG-77     TIME 16:33:02
FILE : CHANG.DSD

ITEM        FIRST POS.  LENGTH  IO-TYPE  MIN.  MAX.  SYMBOLIC DESCRIPTION
SEX             6         1      I 1 2     1     2   1 = MALE
                                                       2 = FEMALE
GRADE          20         1      I 1 0     1     9
SUPRAGLOTTIC   34         1      I 1 0     1     2   1 = YES
                                                       2 = NO
```

4. The query language

In a pilot study using data of patients suffering from carcinoma of the larynx an analysis has been carried out to get an impression of the type of questions needed for a data retrieval. Most of these questions could be characterized by a few keywords:

- Display
- Frequency
- Count
- Table
- Let
- Modify

The first keyword displays the values of some variable for every patient. This Display command as well as all the other commands can be used combined with logical expressions (e.g. display sex if (histological) grade (equals) eq 1). A distribution of a variable is obtained using the Frequency command. Together with the histogram the mean and standard deviations are typed out.

The number of items fulfilling some condition is obtained by the Count command. If one wants to know for example the number of male patients one simply types: count patient-no if sex eq male. Cross tables are obtained using the Table command (see fig. 3). To use this command one has to indicate the number of columns and rows in the table that are required. Moreover for each variable the lowest value used in the table and the class width have to be given.

Fig. 3
Modified T & N classification for 150 patients.

```
REQUEST

TABLE(9,9) WITH T(0,1) AND N(0,1)
```

CLASS NO.	TIS	T1A	T1B	T2A	T2B	T3A	T3B	T4A	T4B	TOTAL
N0	8	31	9	49	8	8	4	2	5	125
N1	0	0	0	0	0	0	0	0	0	0
N2	0	0	1	0	0	0	0	0	0	1
N3	0	0	0	0	0	1	0	0	0	1
N1A	0	0	0	0	0	0	0	0	0	0
N1B	0	2	0	5	0	1	0	1	0	9
N2A	0	0	0	2	2	1	0	1	1	7
N2B	0	1	0	0	0	0	0	0	0	1
NR	0	0	0	2	1	0	0	0	4	7
TOTAL	8	34	10	58	11	11	4	4	10	150

```
REQUEST
```

With the Let command it is possible to make use of functions of the variables defined in the database. For example the NSD can be calculated from the dose per fraction, the elapsed time and the number of fractions using the Ellis formula [5]. One or more of the temporary variables defined with the Let command can be deleted by the Kill command. A maximum of 64 temporary variables are allowed.

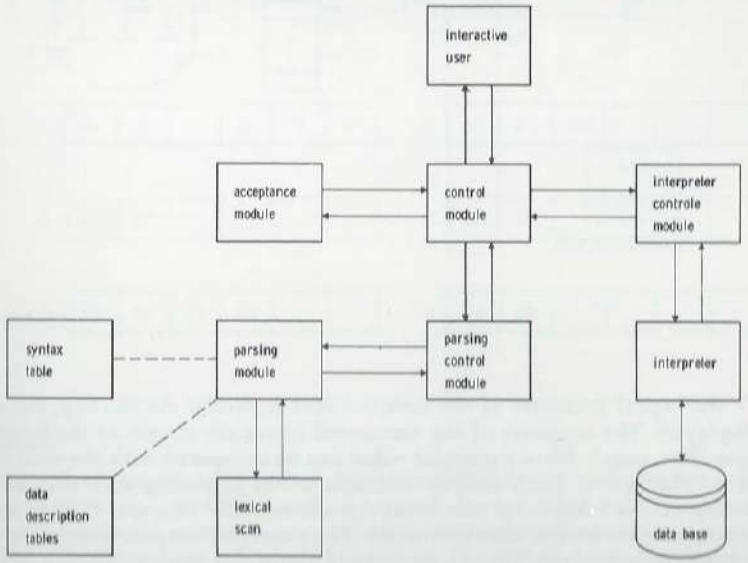
Any modifications that are necessary in the data of a particular patient can be performed with the Modify command. This command makes use of the direct accessibility of the data so that it is not necessary to go through the database in a sequential manner. In fig. 4 some examples are given to indicate the ease with which questions can be asked. As can be seen logical expressions can be used very effectively.

Fig. 4 Some examples of Query Language.

```
COUNT PATIENT_NO  IF NECROSIS .EQ. YES

DISPLAY PATIENT_NO  IF SEX .EQ. FEMALE  .AND. SUPRAGLOTTIC .EQ. NO

TABLE(2,9) WITH SEX(1,1)  .AND.  GRADE(1,1)  IF SEX .EQ. MALE

FREQUENCY GRADE  IF SEX .EQ. FEMALE

LET  DIAGNOSTIC_AGE = DATE_OF_DIAGNOSIS  -  BIRTHDATE

MODIFY NSD = 2001  IF PATIENT_NO .EQ. 53
```

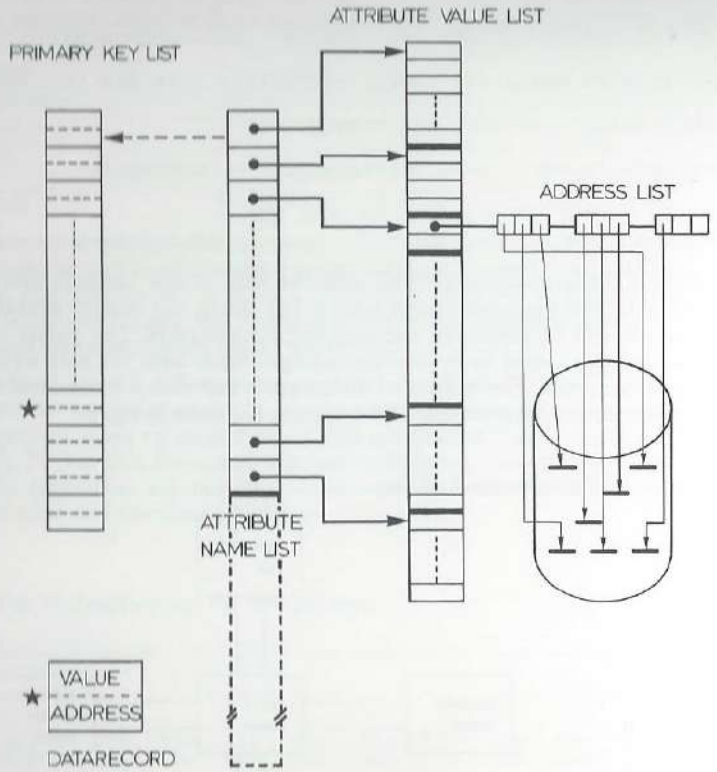
The syntax of the language is defined with the help of the Langpak system. Langpak is an interactive language design system [6]. When the correct syntax is obtained the parser will be driven by the resulting syntax table. The parser receives as its input a sentence typed in by the user and produces with the help of the syntax table a parsed sentence. The output of the parser is in Polish notation and is processed by the interpreter. An overview of the system is shown in fig. 5.

Fig. 5 Overview of the system build-up.



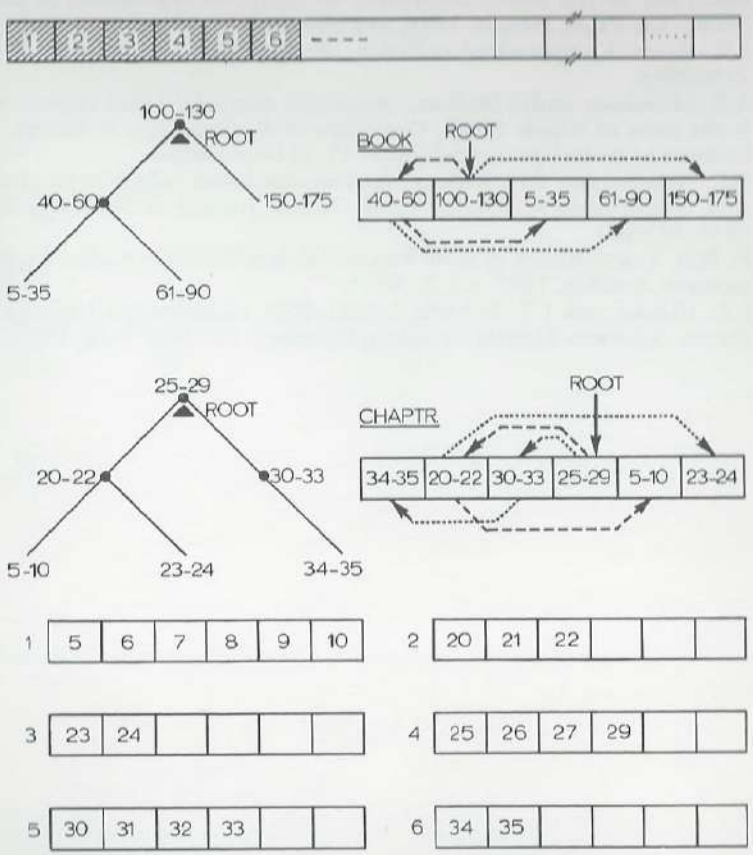
For each record a major key (primary key) has been defined. For this primary key and a small number of other items inverted files are created. A record can be retrieved with a minimum of effort using these inverted files. These inverted files are implemented as balanced binary trees. In fig. 6 the physical structure of the inverted file is outlined. In this figure the variables are called attributes. For each attribute, including the primary key, the values are sorted in the attribute value list. In fig. 6 the primary key list is displayed twice to show the structure of such a list. As can be seen each attribute value is followed by the address of the relevant patient record. In this way it is possible to go through the data base in an efficient way leaving aside non-relevant patient records.

Fig. 6. Physical data structure of inverted files.



In fig. 7 the logical structure of the inverted files is shown. At the top, the sorted list is displayed. The contents of the numbered boxes are shown at the bottom of this figure. The search for a particular value can be compared with the search for a word in a dictionary. Each chapter contains words beginning with the same letter. Starting at the book level one looks for the relevant chapter. Having reached this chapter one looks for the right word. For example, suppose you want to retrieve a value in the inverted file. As mentioned above this inverted file is a balanced binary tree in which each node contains the minimum and maximum values present in a chapter. Similarly each node of the chapter record contains the minimum and maximum values present in a page. So starting at the root of the bookrecord and comparing the search argument with the values at the root one can determine the relevant chapter. In the chapter record one can obtain the right page. In this page the values are displayed together with the patient records to which they belong.

Fig. 7. Logical data structure of the inverted file.



Discussion

An interactive data retrieval system has been designed to fulfil the needs of radiotherapists to have a powerful tool to browse through their data base. In fact the language used in the system is easy to use and non-computer experts learn it very quickly. The advantage of using this system instead of doing handwork is very clear, even if the data base is rather small. The query language can be used for all kinds of data bases. With the help of the data definition language the different data bases are defined and the query language merely has to know with which data base to work. Although the system is written in FORTRAN a MUMPS version will also be implemented. The number of keywords may be extended.

The pilot study proves that the system may fulfil the needs of the radiotherapist. The system makes it possible to be adequately informed about the status of the patients and the success of different treatment policies and methods. Further development shall be forthcoming.

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STELLINGEN

behorend bij het proefschrift van

A.B.M.F. Karim

A CLINICAL REVIEW ON DOSE RESPONSE IN RADIOTHERAPY FOR LARYNGEAL CARCINOMA

Amsterdam, 1 december 1977

1. The parameter T of the recent TNM classifications (U.I.C.C. 1972 and A.J.C. 1976) for laryngeal carcinoma does not appear to be beyond the scope of improvement.

2. Pragmatic radiotherapeutic approaches for laryngeal carcinoma on the question of volume of the primary tumor are not usually encountered. Diagnostic radiology should in future be able to have greater impact on this important topic.

3. Higher dose or greater number of cell kill is not required for a small glottic T1 of TIS carcinoma. But the same may not be true for a T1 supraglottic cancer.

4. From the point of view of radiobiologists, shorter treatment schemes appear to yield better tumor control probability. Economic advantages are also obvious for shorter fractionation schemes. Unfortunately these schemes do not appear to be better at least for the smallest carcinoma of the glottic larynx.

5. 'The fact that the cord does not move after say 4000 rads of cobalt doesn't mean that the tumor is necessarily out of control (by radiotherapy). It may be fibrosis and scarring that causes this lack of mobility. What it does, I think, is impair your judgement ability'.
R.B. Sessions in Panel Discussion: Cancer of the Larynx in Neoplasia of Head & Neck, 1974, 17th Annual Cl. Conf. on Cancer at the Univ. of Texas.

6. Lack of agreement on the characteristics of the (TIS) pre-invasive carcinoma of the larynx amongst some of the pathologists and the clinicians creates misconceptions on this clinico-pathological entity.

7. The contention, "It is apparent that the ideal dose, the ideal time, the ideal fractionation, the ideal protraction are still beyond the reach of the radiotherapist" can no longer be strongly supported in each and every situation.
P. Rubin and G.W. Cassaret in Front. Radiation. Ther. Onc. 3, 33, 1968.

8. "The conclusion which emerges is that although it is too early to generalize, the available evidence for certain types of tumor points to the need for an accuracy of ± 5% in the delivery of an absorbed dose to a target volume if the eradication of the primary tumor is sought. Some clinicians have requested even closer limits such as ± 2% but at the present time it is virtually impossible to achieve such a standard."
I.C.R.U. Report 24: 1977.

9. "The need to make judgments amongst competing treatment modes, as applied to the particularities of a given patient, remains the physicians' central task. How to develop the capacity for a high percentage of right choices is the central question in medical education. . . . I believe we must be much bolder in harnessing the computer as an aid to medical decision-making."
G.J.V. Nossal on Medical Education, Science in the Medical Curriculum in Lancet, October 16, 1976.

10. There is a possibility of media excesses when environmental factors are focussed on:
"That some 90% of cancers are due to environmental factors and thus could be prevented"
Lancet editorial, March 26, 1977
or,
Environmental change before the introduction of antibiotics had a greater effect on health than the activities of hospital doctors and their antibiotics.
A.F. Lever on 'The Role of Medicine'
by Prof. T. McKeown. Lancet, Feb. 12, 1977.

11. Survival of patients with inoperable localized gastro-intestinal carcinoma can be prolonged without major toxicity as much as two fold when optimum doses of effective chemotherapy agents are combined with moderate doses of local radiotherapy.
W. Regelson in Chemotherapy of Gastro-intestinal Cancer,
Int. J. Rad. Oncology Biol. Phys. 1, 109, 1975.

12. "Conflicts between its (Medicine) aims and those of society are increasing. . . . Society has always shaped medicine in the past and is likely to do so in the future. . . . Medicine is simply one of the society's response to its environment. . . . The doctor has a place in society which is enviable. They can destroy it by exaggeration, unnecessary protest and a failure to understand themselves and the society within which they function."
P. Rhodes in 'The Value of Medicine', 1977 (Allen & Unwin, London).