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CARCINOMA OF THE LARYNX

II. Treatment by ^{60}Co supervoltage irradiation

by

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The radiotherapy of carcinoma of the larynx has been changed in the course of the past decade almost everywhere to supervoltage irradiation. Owing to the short follow-up periods, little is yet known of the results, but the relatively few reports seem promising.

These neoplasms commenced to be treated by us with a ^{60}Co unit of kilocurie strength around 1 August 1963. The results obtained during a 5-year period with this unit have been analysed and the expected crude 5-year survival calculated. The object of the present communication is primarily to submit these results, but they will also be compared with those in a group of patients treated during the preceding period primarily by conventional irradiation. Lastly, the authors will discuss the possible causes of recurrences following radiotherapy.

Material. A total of 153 patients with carcinoma of the larynx was admitted from 1 August 1963 to 1 August 1969. However, the present material includes only 152 patients, as one died of an intercurrent disorder before treatment of the larynx had been started. Apart from the exclusion of this patient, the material is unselected.

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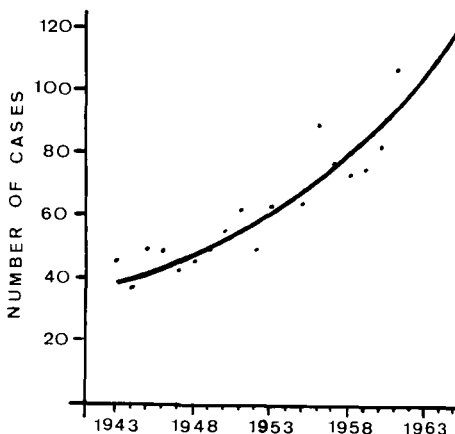


Fig. 1. Annual number of cases of carcinoma of the larynx notified to the Danish Cancer Registry. The 'average curve' indicates the presumed number of notifications in 1965.

Incidence. The last publications of the Danish Cancer Registry contained 82 cases of carcinoma of the larynx in 1960 and 107 cases in 1961 (CLEMMESEN & SØRENSEN 1965). No reports have as yet appeared on the annual number of new cases during the period 1963—1968, but it is estimated to be about 120. This estimate is based upon the number of new cases notified annually during the period 1943—1961 (cf. Fig. 1). The Radium Centre serves a geographic area comprising Jutland (except for the area south of Kongeåen) corresponding to a population of 1.2 millions. Table 1 indicates that approximately 30 patients are referred annually, in exact agreement with the number expected from an area housing about a quarter of the Danish population. These figures support the assumption that the material is representative of a geographic area having a population of 1.2 million. The annual incidence of the disease per 100 000 of the population is then 2.5 (or 1 : 40 000).

Sex ratio. Nine per cent of the patients were women (16/153) and 91 per cent were men (136/152).

Age distribution. The age distribution is given in Fig. 2. The youngest patient was a woman of 26 and the oldest a man of 90, average age at time of histologic diagnosis being 60 years and 1 month.

Histology. Histologic examination revealed squamous cell carcinoma in 151 patients and malignant columnar cell adenoma in one patient. Eight patients were classified as having carcinoma in situ, all with definite epithelial carcinomatous changes but no evidence of invasive growth.

Table 1

The 152 patients of the present material grouped according to year of treatment (from August to August) and follow-up period so as to calculate the mortality coefficients for the individual years

Year of treatment	Number of patients	Number of survivals after				
		1 year	2 years	3 years	4 years	5 years
1963/64	24	23	20	20	20	18
1964/65	34	29	26	25	23	
1965/66	29	27	22	21		
1966/67	41	36	34			
1967/68	24	19				
Total	152	134	102	66	43	18
Number of deaths		18	13	2	2	2

Symptoms and signs. The primary sign was hoarseness in 80 % of the patients (121/152) and irritation in the throat with pain radiating to the homolateral ear in 13 % of the patients (20/152). In the remaining 11 patients the primary signs were cough, dysphagia, enlargement of cervical lymph nodes, or dyspnoea. The interval from the onset of the primary symptom or sign until the histologic diagnosis was less than 4 months in 41, 4 to 8 months in 32, and more than 8 months in 27 of the patients.

Classification. The TNM system in the form suggested by UICC (1968) was used. Table 2 gives the classification of the 152 patients divided into three main groups: supraglottic 41 patients (27 %), glottic 102 patients (67 %), and subglottic 9 patients (6 %). As is apparent from Table 2, a total of 17 patients (11 % or 17/152) had presumed lymph node metastases on admission. Within the three main groups the incidence of cervical node metastases was as follows: supraglottic 28 % (11/41), glottic 3 % (3/102), and subglottic 33 % (3/9).

Method of treatment. The primary therapeutic principle was almost invariably radiotherapy, 147 patients having been treated primarily by radiotherapy and 5 by surgery. All the 147 patients were treated by a ^{60}Co unit of kilocurie strength; FSD was 80 cm. In the early treatment period the field sizes were often 4 cm $\times$ 4 cm and 4 cm $\times$ 5 cm, but during the last three years never less than 6 cm $\times$ 6 cm. The field size was extended when necessitated by the size of the tumour or by nodal metastases.

A treatment shell was made for each patient and in this he was fixed, both during the simulation and the treatments. The treatment shell was composed of

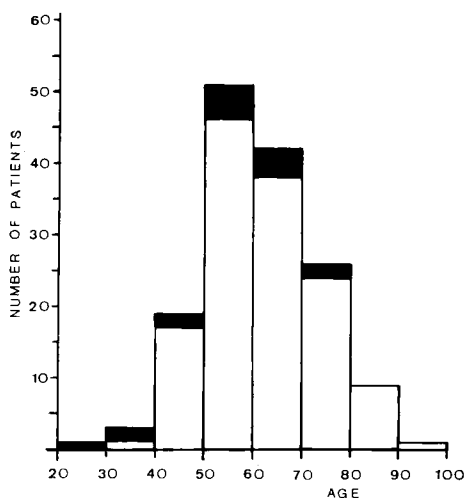


Fig. 2. Age distribution at time of histologic diagnosis. Black column represents women and white column men.

two parts, a posterior part made of plaster and an anterior part of plastic; these were fastened together during the treatment, the plastic part being fastened to the former part. A hole was cut in the plastic corresponding to the treatment fields, the marking of the field being done with the aid of a so-called simulator — a fluoroscopic apparatus whose roentgen tube is placed in exactly the same position as the head of the ^{60}Co unit. A correct placement of the fields was secured by control photographs of the marked area. The dose distribution was calculated for each patient.

A compensation filter was used to secure a homogeneous dose in the irradiated area in 26 patients, in nearly all of whom the fields were large. Treatment was administered on 5 days of the week to one or two opposing fields; a central tumour dose of 6 000 rad over 6 weeks was the aim. Extensive subglottic carcinoma in 3 patients and large glottic tumours with respiratory distress in 2 patients indicated primary surgery.

Follow-up. Each patient's reactions were closely observed daily by indirect laryngoscopy during radiotherapy. Any suggestion of residue resulted in the patient being admitted about 8 weeks after the completion of the radiotherapy for direct laryngoscopy and possibly biopsy; a positive biopsy specimen indicated supplementary surgery. Patients with no signs of residual tumour or recurrence were controlled on an out-patient basis in a collaboration between the radiotherapists and otologists. The follow-up will be continued for at least 10 years.

Table 2

TNM classification of 152 patients with carcinoma of the larynx, treated at Århus from 1 August 1963 to 1 August 1968

		Group				Total
		N0	N1	N2	N3	
Supraglottic	T1	6				
	T2	7				
	T3	9	3			
	T4	8	2	4	2	41
Glottic	T1	39				
	T2	15				
	T3	42				
	T4	3	3			102
Subglottic	T3	3	1			
	T4	3		1	1	9

Therapeutic results. The authors, to express the result of the treatment, calculated the expected crude 5-year survival rate on the lines recommended by NOHRMAN (1953). The material was first divided as in Table 1. The mortality coefficients for the individual years of the follow-up period were then calculated with the formula

$$Q_n = \frac{d_n}{d_n + l_n}$$

where Q_n is the mortality coefficient in the n' th year, d_n the number of deaths in the n' th year, and l_n the number of patients alive at the end of n' th year. The 5 Q -values are then inserted into the formula

$$100 \times (1 - Q_1) (1 - Q_2) \dots (1 - Q_n)$$

the resulting value being the calculated crude 5-year survival rate. The results of the calculations are plotted as a survival curve in Fig. 2, the calculated crude 5-year survival rate being 65 %. However, this figure carries some uncertainty, partly as only a limited number of patients have a follow-up period exceeding 5 years and partly as two deaths from carcinoma took place in the 5th year (cf. Table 1). A more correct expression of the 5-year result in the material would be obtained by extrapolating the curve corresponding to the 5th year of the follow-up period. As is apparent from Fig. 2, the expected 5-year result is then 70 %. The standard error was calculated on the 3-year result by the Greenwood formula (UICC 1969)

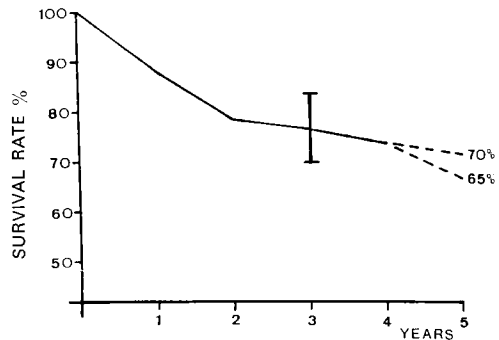


Fig. 3. Survival curve for 152 patients with carcinoma of the larynx. The standard error calculated and marked twice on the curve.

$$P_n \sqrt{\sum \frac{l - p_i}{n_i p_i}}$$

where P_n is the survival rate for the n 'th year, p_i the survival rate during the i 'th year for patients alive at the beginning of that year, n_i the corresponding number of patients, and Σ the summation of the values for the individual years. The standard error was 3.51 %; thus $2 \times$ the standard error is 7 % as plotted in Fig. 3.

Owing to the short follow-up periods the results in the individual groups have not yet been analysed. It may, however, be mentioned that the expected 5-year results for the 39 T1N0M0 glottic carcinomas is 97 %, one patient having died 6 months after the treatment without signs of recurrence in the larynx or the neck, but with large mediastinal metastases, presumably due to carcinoma of the lung.

Vocal results. The authors chose patients, followed for more than 2 years and who had managed with radiotherapy as the only treatment, to assess the quality of the voice after ^{60}Co therapy. This group comprised a total of 68 patients: 61 (90 %) had normal voice function (although several had some deterioration in quality), 6 (9 %) could speak but the quality was distinctly debased and 1 (1 %) was totally aphonic.

Side effects of radiotherapy. Irritation and dryness of the pharyngeal mucosa occurred in the majority of the patients during the treatment period and the first months after its completion. These symptoms were moderate and transient; only 2 patients had marked complaints for more than two years. One patient had to have tracheotomy during the treatment because of a laryngeal reaction consisting of oedema and respiratory distress. On the other hand, tracheotomy

had been necessary before the treatment in 4 patients because of difficulty in breathing.

Acute radiodermatitis did not occur. One patient had necrosis of the skin and anterior part of the thyroid cartilage leading to a fistula — presumably because of a complicating abscess in the area. A small number of the patients exhibited subcutaneous fibrosis although this was never bothersome.

Perichondritis of varying severity was observed in some of the patients with recurrences. It rarely occurred, was mild and disappeared a few months after the treatment in patients without recurrences. Perichondritis never necessitated laryngectomy.

Surgical aspects. Primary total laryngectomy, as already mentioned, was performed in 5 patients, because of large subglottic tumours in 3 and glottic neoplasms with respiratory distress in 2 patients.

So far (up to 1 August 1969) 60 recurrences after radiotherapy have occurred in the material, and of these patients 53 have been treated surgically. The operations were distributed as follows: 2 patients were subjected to cordectomy, 7 to partial laryngectomy, 2 to partial laryngectomy and later total laryngectomy, 25 to total laryngectomy, 23 to total laryngectomy and dissection of cervical nodes, and 4 to dissection of cervical nodes.

Operative complications were few and no deaths due to operation occurred. Severe infection or major necrosis did not occur. Eight of the 40 patients subjected to laryngectomy developed fistulae to the hypopharynx or oesophagus; six of these were transient, and only two required one or more corrective operations.

Frequency of laryngectomy was calculated for patients followed for at least 3 years to obtain a numerical expression of how large a proportion lose laryngeal function. This frequency was found to be 24 % (21/87).

An attempt was made to compare the results of primary radiotherapy with a conventional unit and a ^{60}Co unit of kilocurie strength. A total of 115 patients were treated for carcinoma of the larynx during the period 1949—1959; of these 96 were primarily irradiated by a conventional unit. This group was compared with the 85 patients who were primarily irradiated by a ^{60}Co unit of kilocurie strength during the period 1963—1966. The results are given in Fig. 4 which indicate that the therapeutic results for the ^{60}Co group are better than those for the conventional group, assessed on the basis of the survival curve. The gain is modest and far from significant, but at the same time it must be emphasized that the two materials are not comparable in respect to

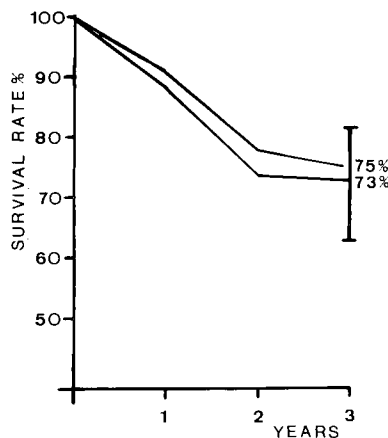


Fig. 4. Survival curves for two groups of patients, the upper representing a group treated by ^{60}Co supervoltage and the lower curve a group treated by conventional roentgen therapy.

classification, as evident from Table 3. The ^{60}Co group includes a relatively larger number of advanced conditions than the conventional group. If the number of T4N0M0 cases + the number of cases having nodal metastases (N1 + N2 + N3 cases) is expressed as a percentage of the total number within each of the two groups, the following figures are obtained: conventional group 11 % (11/96) and ^{60}Co group 21 % (18/85). The two groups might be rendered comparable by exclusion of analogous groups, e.g. by excluding the advanced cases from both groups. This was tried, but failed to lead to comparability. The two materials are otherwise comparable as regards symptoms and signs, sex ratio, age distribution, and average age at the time of histologic diagnosis.

A good expression of the therapeutic efficacy is how large a proportion of the patients are cured by irradiation alone. The 3-year cure rate in the two groups following irradiation alone was 57 % (55/96) in the conventional group and 59 % (50/85) in the ^{60}Co group. It must, however, be borne in mind that the ^{60}Co group comprises a considerably larger number of advanced conditions.

Recurrences. Sixty out of 147 primarily irradiated patients developed recurrences within the control period. The case records were perused with a view to finding possible reasons why radiotherapy failed. Particular interest was centred on possible technical causes due to underdosage in the area of the tumour or field adjustment, dosage planning, or divergences in the dose-time relation. After this perusal the site of the recurrences was related to the above factors, especially those that might have caused underdosage in part of the tumour area. The possible causes of the recurrences are listed in Table 4. Of

Table 3

Comparison of TNM classification of 96 patients treated by roentgen irradiation and 85 patients treated by ^{60}Co irradiation

		96 patients treated by roentgen irradiation				85 patients treated by ^{60}Co irradiation			
		N0	N1	N2	N3	N0	N1	N2	N3
Supraglottic	T1	4	1	1		4			
	T2	6	1			5			
	T3	8	1	1		6	2		
	T4	2	3			3	2	3	2
Glottic	T1	33				19			
	T2	14				13			
	T3	19				18			
	T4	1				1	3		
Subglottic	T3	1				2			
	T4					1	1		

course, this table must be accepted only with reserve, as there was often the question of an estimate. The most important presumed cause is submitted and tabulated for each individual patient; several factors may have arisen but this could not be tabulated.

It is apparent from the table that in 20 patients (groups 1 to 8), i.e. 33 %, there may be a suggestion that purely technical causes were to blame. On further investigation, however, it would appear that there can have been only 7 patients, i.e. 11 % (7/60), in whom technical reasons could be said with certainty to have produced local underdosage.

The dose-time relation was also re-evaluated. As already mentioned, the planned radiation dose for curative purposes was 6 000 rad administered in 5 fractions weekly during a total period of about 42 days. A considerably lower total dose (4 700, 3 700, 5 300 rad) was administered to 3 patients (group 10), in 2 of whom the treatment had to be interrupted because of severe local symptoms; in the third patient the treatment had been planned as palliation right from the start.

Ten patients in group 9 were treated over a longer period than the normal approximately 6 weeks without a compensatory increase of the originally planned dose of about 6 000 rad. The treatment in 3 patients had been temporarily interrupted because of endolaryngeal reaction and in another 7 patients by Christmas, Easter, or Whitsun. It cannot be claimed with certainty that these factors were the cause of the recurrences.

Table 4

Possible causes of treatment failure in 60 patients, all with recurrences, after primary radiotherapy of 147 patients

Cause of failure	Group	Number of patients
Technical	1 — Small field size with underdosage posteriorly in the larynx	4
	2 — Small field size with possible underdosage posteriorly in the larynx	1
	3 — Small field size with underdosage anteriorly in the larynx	1
	4 — Small field size with possible underdosage anteriorly in the larynx	3
	5 — Normal field size with underdosage posteriorly in the larynx	2
	6 — Normal field size with possible underdosage posteriorly in the larynx	4
	7 — Use of compensation filter with possible underdosage anteriorly in the larynx	2
	8 — Small field size with correct placement	3
Dose-time relation	9 — Strikingly long treatment period	
	A. Due to endolaryngeal reaction	3
	B. Christmas, and other holidays	7
	10 — Small radiation dose	
'Tumour-bio-logic'	A. Palliation	1
	B. Treatment interrupted due to reaction	2
	11 — Recurrence in cervical lymph nodes outside treatment field	4
	12 — Recurrence in mediastinum	2
	13 — Recurrence in lungs	1
	14 — Malignant adenoma, hardly radiosensitive	1
	15 — Widespread carcinoma	11
	16 — No explanation	8

This leaves a major group of recurrences (groups 11 to 16), a total of 27 patients, in whom the recurrence appeared outside the treated area or in whom the growth had been locally much advanced. In these latter a reduced oxygen tension in the large neoplasm may have been a cause of reduced radiosensitivity and thereby of the recurrence.

No demonstrated or conceivable explanation of the recurrence is evident in the last group of 8 patients (group 16).

Discussion

The analysis of the 5-year material failed to disclose any surprising factors as regards the histology, sex ratio, age distribution, symptomatology, or TNM classification as compared with the findings during the period prior to 1 August

1963 (JØRGENSEN 1970). However, there was a relative increase in the number of advanced conditions although without any evidence of a change in the pattern of the disease.

The analysis was carried out by the procedure recommended by NOHRMAN (1953). This is closely related to the actuarial method of UICC, but requires a 100 % control. It fails to utilize the material quite as well as the actuarial method, but is easier in practice as it does not presuppose a status for all the patients on a given day. The actuarial method would require for the present material the status for all the patients on 1 August 1969, and this would have involved a great deal of extra work. NOHRMAN's procedure also permits correction for mortality from causes other than carcinoma. In the future the patients' data will be stored and computer analysed. When operating with materials having a 100 % follow-up, NOHRMAN's method for calculating the survival curve at any time is presumably best applicable in practice.

Extrapolation, as mentioned, had to be done of the last part of the survival curve (Fig. 2) because of the small number of patients with a 5-year follow-up period and two deaths during the 5th year of follow-up which deteriorate the result disproportionately. The extrapolation was felt to be permissible, as in major series the survival curve after the 3rd year has proved to be practically a straight line, determined by the mortality in the population from causes other than carcinoma of the larynx + a few late deaths from that condition (TASKINEN 1969, JØRGENSEN 1970). The expected 5-year survival result of 70 % will be checked and published in four years time.

Few publications of materials from recent years on the supervoltage therapy of carcinoma of the larynx have appeared but the results seem promising (DAHL et coll. 1964, CAVANAUGH et coll. 1968, HIBBS et coll. 1969).

Supplementary secondary surgery after ^{60}Co irradiation posed no special problems. The frequency of laryngectomy proved to be low (24 % in patients with a minimum survival of 3 years) and is not expected to have reached 30 % when a 5-year follow-up period has been obtained for all patients, as only a few late laryngectomies are being done.

In U.S.A., in particular, there has been a marked trend towards primary surgery. However, without analyses from that country of the same nature and from the same period as the present one, it is difficult to compare the two procedures. ALEXANDER (1966), SMITH (1966), SPENCER (1967), VON ESSEN (1968) and HUTCHINSON (1968) have published series from U.S.A. from the 1950's up to the beginning of the 1960's. The composition as regards classification does not appear to differ much from ours; the frequency of total laryngectomy in these series ranged from 55 to 75 %. The survival figures in the present material compare favourably. The procedure of primary radio-

therapy of carcinoma of the larynx therefore appears to be a better method, both as regards survival and preservation of laryngeal function.

As already mentioned, an attempt was made to compare the present material with one of patients who had been treated primarily by conventional radiotherapy. However, the two materials were not comparable as the ^{60}Co material included a considerably larger number of advanced neoplasms. Nevertheless the survival curve for the ^{60}Co group was better although not significantly so (Fig. 4). Radiotherapy with a ^{60}Co unit of kilocurie strength and a simulator for marking the fields and individually tailored, fixed treatment shells thus seems to be superior to conventional radiotherapy.

Analysis of the 60 recurrences after radiotherapy indicated that technical factors might have contributed to the recurrence in 33 % of the patients. However, divergences in the field technique occurred only during the first 3 years of the 5-year period. It is pointed out also that an altered fractionation of the dose, prolonging the treatment period because of Christmas and other holidays, may have exerted an influence upon the recurrence. A careful field technique and due regard to the dose-time relation ought to improve the therapeutic results further.

Conclusion

A material of 152 patients with carcinoma of the larynx is presented; 147 of these were primarily treated by irradiation with a ^{60}Co unit of kilocurie strength during the period 1 August 1963 to 1 August 1968. The expected crude 5-year survival result was calculated to be 70 % and the frequency of laryngectomy for recurrence was 24 %. These results were compared with those in a group of patients treated by conventional roentgen therapy. The survival curve for the ^{60}Co -treated patients was better in spite of the fact that this group included a relatively larger number of advanced conditions.

Perusal of the records of 60 patients with recurrence following radiotherapy revealed that technical causes (field size and placement) might possibly have contributed to this failure in a third of the patients. Definite technical causes were demonstrable, however, in only 7 of the patients, or 11 % (7/60).

The results are compared with recent materials from U.S.A. treated predominantly by surgery. Primary radiotherapy appears to afford better survival results, and in addition twice as many patients by avoiding laryngectomy preserve laryngeal function.

The method of calculation in working out the survival curves is discussed. The 'Nohrman method' used in the present investigation proved easy and is presumably better for future computer analysis than the actuarial method recommended by UICC.

SUMMARY

The results of the primary treatment of 147 patients with carcinoma of the larynx with a ^{60}Co unit of kilocurie strength during a 5-year period are reported and compared with those in a material treated by conventional roentgen therapy. It is evident that primary radiotherapy appears to provide better survival and improved laryngeal results than laryngectomy.

ZUSAMMENFASSUNG

Die Resultate einer vergleichenden Untersuchung von 147 Patienten mit Kehlkopfkarcinom nach primärer Behandlung mittels einer ^{60}Co -Anlage von Kilocuriestärke und mittels gewöhnlicher Röntgenbestrahlung werden berichtet. Es zeigte sich, dass die primäre Strahlenbehandlung eine längere Überlebenszeit und bessere Kehlkopfsfunktion als Laryngektomie aufweist.

RÉSUMÉ

Les auteurs présentent les résultats du traitement primitif du cancer du larynx pendant une période de cinq ans sur 147 malades au moyen d'une unité de cobalt-thérapie d'un kilocurie et les comparent avec les résultats de sujets traités par la roentgen-thérapie classique. Il est évident que la radio-thérapie primitive paraît donner une meilleure survie et des résultats laryngés meilleurs que laryngéctomie.

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