

LARYNGEAL CARCINOMA

I. Treatment results

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Supervoltage techniques were in most countries introduced during the fifties, for irradiation of laryngeal carcinoma. The treatment results from the period 1963 to 1968 in Århus have been reported previously (JØRGENSEN 1974). During the years 1968 to 1972 an additional 204 patients were treated. The purpose of the present communication is primarily to submit the further treatment results. It is also the intention to report on the total series of 359 patients as an introduction to biologic and microscopic analyses in forthcoming communications (HJELM-HANSEN et coll. 1979, LUND et coll. 1979).

Material and Methods

During the period August 1963 to August 1968, 152 patients with previously untreated carcinoma of the larynx were admitted to the Radium Centre of Århus and revision of the records added a further 3 marginal cases, totalling 155 cases. The revision was performed because of the new TNM rules (AJC, UICC, 1972), which include the marginal zone. During the period August 1968 to August 1972 204 new patients were admitted, giving a total of 359 patients from 1963 to 1972; 357 had epidermoid carcinomas and 2 adenocarcinomas. All data were collected, controlled and analysed by computer in December 1976. All survival rates were calculated according to information from the Danish People's Register as per 10th January 1977.

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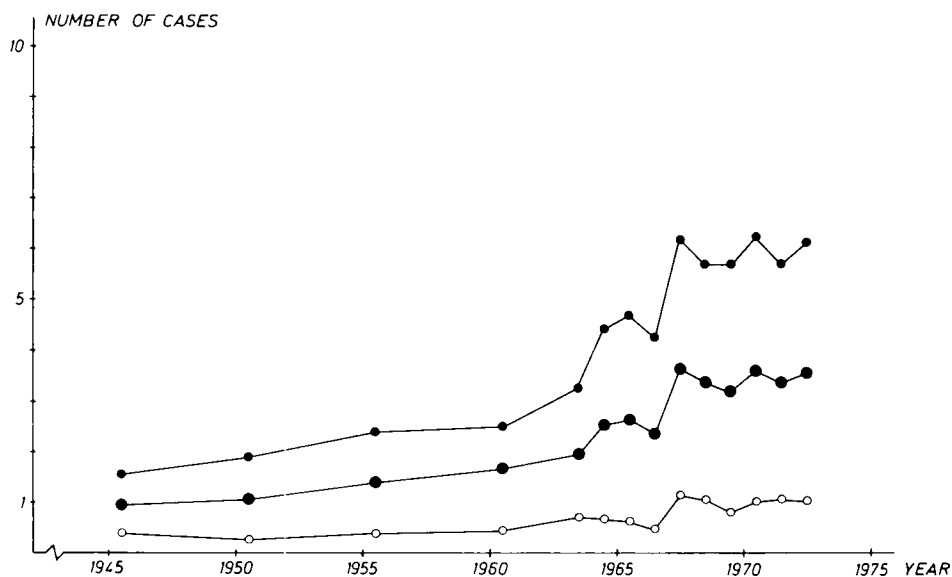


Fig. 1. Incidence of carcinoma of the larynx in Denmark 1943 to 1972 per 100 000 inhabitants. ● male. ○ female. ● total.

Incidence. A calculation of the incidence (crude) of the disease in Denmark shows a distinct difference between the sexes, the incidence in women being clearly lower (Fig. 1). A more than threefold increase of the incidence took place for both sexes between 1943, when the Danish Cancer Register (CLEMMESSEN 1974) was founded, and 1972. An analysis of coded records from the Danish Cancer Register in the period 1963 to 1968 showed that the series was very close to being representative of a certain geographic area, i.e., Jutland except for the area south of Kongeåen (JØRGEN-

Table 1

Age and sex distribution

Age	Supraglottic		Glottic		Subglottic
	Female	Male	Female	Male	Male
<30	—	—	1	—	—
30-39	1	—	2	3	—
40-49	3	16	2	16	1
50-59	7	34	12	64	3
60-69	6	18	5	73	3
70-79	4	16	2	42	2
80-89	—	4	1	11	3
>90	1	1	—	2	—
Total	22	89	25	211	12

Table 2
TNM classification (UICC, AJC 1972) of the tumours treated 1963-1972

	N0	N1a	N1b	N2a	N2b	N3	Total
Supraglottic							
T1a	13	—	—	—	—	—	13
T1b	18	2	2	—	—	—	22
T2	18	1	1	—	1	—	21
T3	10	—	6	1	2	3	22
T4	13	1	12	—	3	4	33
Total	72	4	21	1	6	7	111
Glottic							
T1S	19	—	—	—	—	—	19
T1a	82	—	—	—	—	—	82
T1b	25	—	—	—	—	—	25
T2	63	—	1	—	—	—	64
T3	31	—	4	1	—	—	36
T4	7	—	2	—	—	1	10
Total	227	—	7	1	—	1	236
Subglottic							
T2	2	—	—	—	—	—	2
T3	1	—	1	—	—	—	2
T4	6	—	—	—	1	1	8
Total	9	—	1	—	1	1	12

SEN 1976). During the years 1968 to 1972 no change took place, and hence the total series may be considered to be representative of the area mentioned.

Sex ratio. Thirteen per cent of the patients were females (47/359) and 87 per cent males (312/359). In the last period, 1968 to 1972, the corresponding figures were 15 and 85 per cent.

The age distribution appears in Table 1, which shows that the incidence of the disease is highest for persons around the age of 60 and that it is relatively higher among women in the younger age groups.

Symptoms and signs. Hoarseness was the primary symptom in 97 per cent (229/236) of the patients with glottic carcinomas, in 48 per cent (53/111) of the patients with supraglottic carcinomas and in 10 of the 12 subglottic cases. Irritation in the throat with pain eventually radiating to the homolateral ear was the first symptom in 39 per cent (43/111) of the supraglottic cases. In the remaining 24 patients the primary symptoms or signs were cough, dysphagia, enlargement of cervical lymph nodes or respiratory obstruction.

Table 3*Site of origin (percentage in parentheses)*

Supraglottis	
Epilarynx, post. surface of suprahyoid epiglottis	24 (22.6)
Aryepiglottic fold	18 (16.2)
Arytenoid	3 (2.7)
Infrahyoid epiglottis	20 (18.0)
Ventricular bands	44 (39.6)
Ventricular cavities	2 (1.8)
Total	111 (100.0)
Glottis	
Vocal cords	231 (97.9)
Anterior commissure	4 (1.7)
Posterior commissure	1 (0.4)
Total	236 (100.0)
Subglottis	12 (100.0)

Table 4*Primary treatment*

	Supraglottic	Glottic	Subglottic
Irradiation	108	223	8
Irradiation interrupted by total laryngectomy	—	1	—
Total laryngectomy	—	3	2
Total laryngectomy and neck dissection	1	3	2
Stripping	—	3	—
No treatment	2	3	—
Total	111	236	12

Classification and site of origin (Tables 2, 3). The classification was made according to the rules of UICC and AJC (1972). It appears that 12.5 per cent (45/359) of the patients had possible lymph node metastases on admission, the incidence being highest in the supraglottic group, 31 per cent (34/111), and lowest in the glottic group, 3 per cent (8/236). In the subglottic group 3 of 12 patients had primary lymph node metastases. The assessment of the site of origin in each individual patient is presented in Table 3.

Method of treatment (Table 4). The majority of the patients were irradiated as the primary treatment. The source of radiation was a ^{60}Co apparatus of kilocurie strength. The SSD was 80 cm. Apart from the first years of the period the field size was never less than 6 cm \times 6 cm. A treatment shell was made for each patient and a

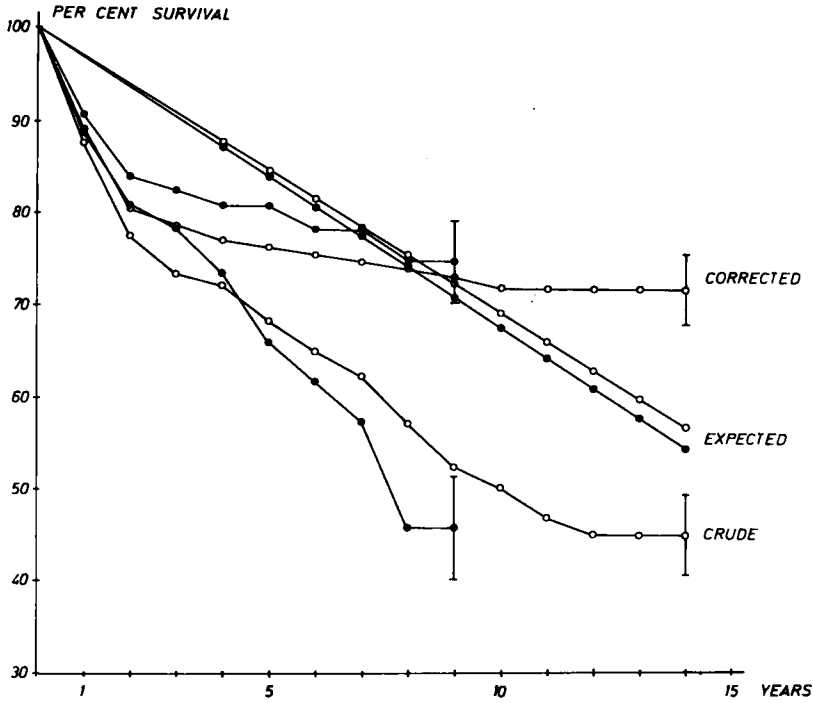


Fig. 2. Survival curves for 359 patients with carcinoma of the larynx. Standard error is marked in the curves. ○ 1963 to 1968 (155). ● 1968 to 1972 (204).

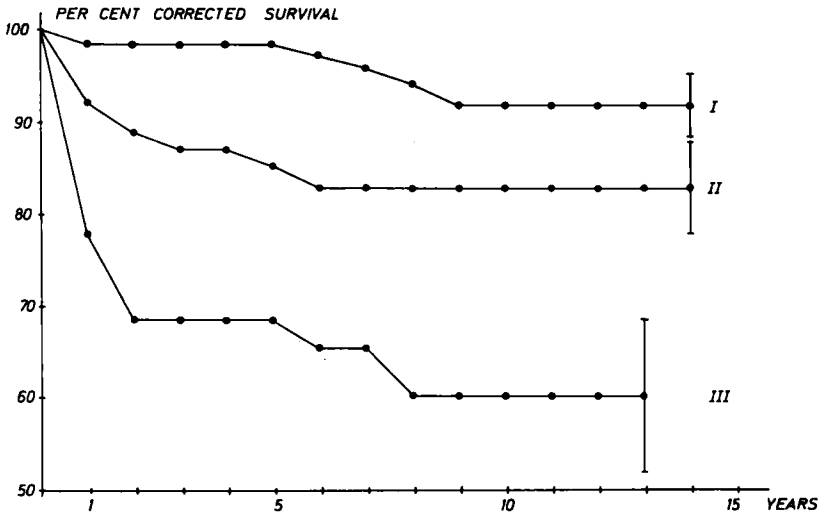


Fig. 3. Survival curves, corrected for mortality from other causes than carcinoma of the larynx, in glottic stage I (126), II (63) and III (46) cases. Standard error is marked in the curves.

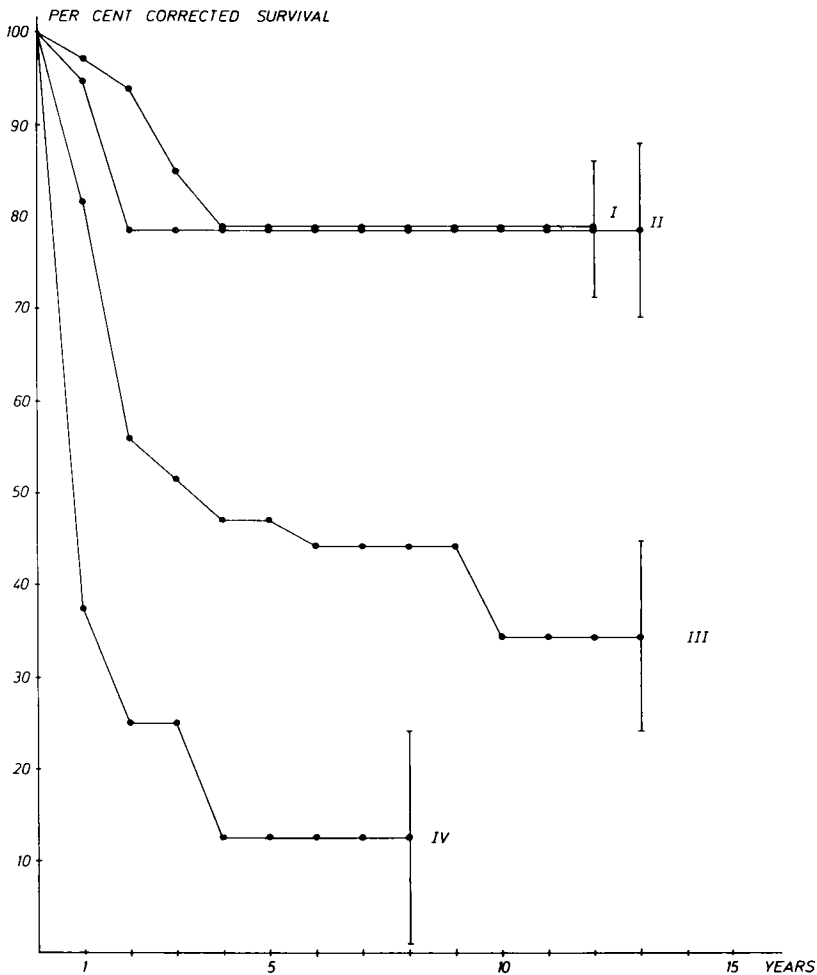


Fig. 4. Survival curves, corrected for mortality from other causes than carcinoma of the larynx, in supraglottic stage I (33), II (19), III (51) and IV (8) cases. Standard error is marked in the curves.

simulator technique was used. The method of ^{60}Co irradiation was changed in 1970, both fields being irradiated every day, and the central tumour dose raised from 57 Gy to 60 Gy. The aim was to administer 30 fractions over 6 weeks. For further description of the radiation technique, surgery in case of recurrence and follow up, cf. JORGENSEN & SELL (1971) and JORGENSEN (1974). All patients were observed from 4 to 13 years.

Results

The survival curves of the two periods before and after 1968 were calculated (as of 12th January 1977) according to the actuarial method (UICC 1969, BERKSON &

Table 5

Time of occurrence of local recurrence and lymph node metastases

Years of observation	Local recurrence		Lymph node metastases*	
	Glottic	Supraglottic	Glottic	Supraglottic
0-1	44 ^a	43 ^b	12 ^c	20 ^d
1-2	10	9	1	6
2-3	5	1	3	1
3-4	4	1	2	—
4-5	1	2	—	1
5-6	1	—	1	—
6-7	1	—	—	—
7-8	—	1	1	—
8-9	3	—	—	—
9-10	1	—	1	—
Total	70	57	21	28

* Secondary lymph node metastases and the primary ones not removed by primary treatment.

^a includes 13 residual tumours.

^b includes 19 residual tumours.

^c includes 3 cases with primary lymph node metastases.

^d includes 15 cases with primary lymph node metastases.

GAGE 1950), and correction for mortality from causes other than laryngeal carcinoma was carried out by calculating the corrected mortality coefficients for the separate years. The expected survival curves express the expected survival of a group of persons having the same distribution of age and sex, calculated on the basis of the statistics concerning the population of the whole of Denmark (Statistisk Årbog 1963-1972). Greenwood's formula was used for calculating the standard errors (UICC 1969).

It is evident that no differences as to 5-year crude survival rate could be traced between the two periods, the 5-year crude survival rate for the first period being 68 per cent, and 67 per cent for the last period (Fig. 2). However, the curve from the period after 1968 corrected for mortality from causes other than carcinoma is placed at a higher level indicating a higher cure rate. It is obvious that the improvement is not statistically significant.

Figs 3 and 4 show the survival curves corrected for mortality from causes other than laryngeal carcinoma in the glottic and the supraglottic groups, respectively. The curves are an expression of the cure possibilities. It is seen that mortality in the malignant disease dominates the first 2 to 3 years, except in the glottic group, stage I.

Local recurrence. Residual tumour or local recurrence developed in 135 patients, i.e., 70 glottic, 57 supraglottic and 8 subglottic cases. The appearance time after

Table 6*Frequency of total laryngectomy (percentage in parentheses)*

	Years of observation	No. of total laryngectomies/ No. at risk
Primary total laryngectomy	4	11/359 (~ 3.1)
Secondary total laryngectomy	4	82/359 (~ 22.8)
Primary + secondary total laryngectomy	4	93/359 (~ 25.9)
Secondary total laryngectomy	5	73/320 (~ 22.8)
	6	62/272 (~ 22.8)
	7	51/223 (~ 22.9)
	8	44/179 (~ 24.6)
	9	30/139 (~ 21.6)
	10	25/106 (~ 23.6)

Laryngectomized patients alive after 4 years of observation 52 % (48/93), dead of carcinoma of the larynx 40 % (37/93) and other causes 8 % (11/93).

Table 7*Frequency of total laryngectomy and stage of disease (percentage in parentheses)*

	Supraglottic	Glottic
Stage I	10/33 (30.3)	8/126 (6.4)
Stage II	4/19 (21.1)	18/63 (28.6)
Stage III	23/51 (45.1)	15/46 (32.6)
Stage IV	0/8 (—)	1/1 (—)
	37/111 (33.3)	42/236 (17.8)

In the subglottic group total laryngectomy was performed in 3 patients (2 in stage II and 1 in stage III).

primary treatment in the glottic and supraglottic groups (Table 5) is characterized thereby, that most local recurrences appear during the first 2 years of observation, i.e., 83 per cent (106/127).

Lymph node metastases. On admission 12.5 per cent (45/359) of the patients had lymph nodes clinically assumed to be involved. Table 5 shows the time of occurrence of primary and late lymph node metastases, the subglottic group again being omitted. The frequency of involvement of lymph nodes was highest in the supraglottic group, being 42 per cent (47/111) (34 primary lymph nodes, Table 1 and 13 late ones, Table 5).

Frequency of partial and total laryngectomy (Table 6). During the period of observation 24 partial and 93 total laryngectomies were performed. Hence the frequency of

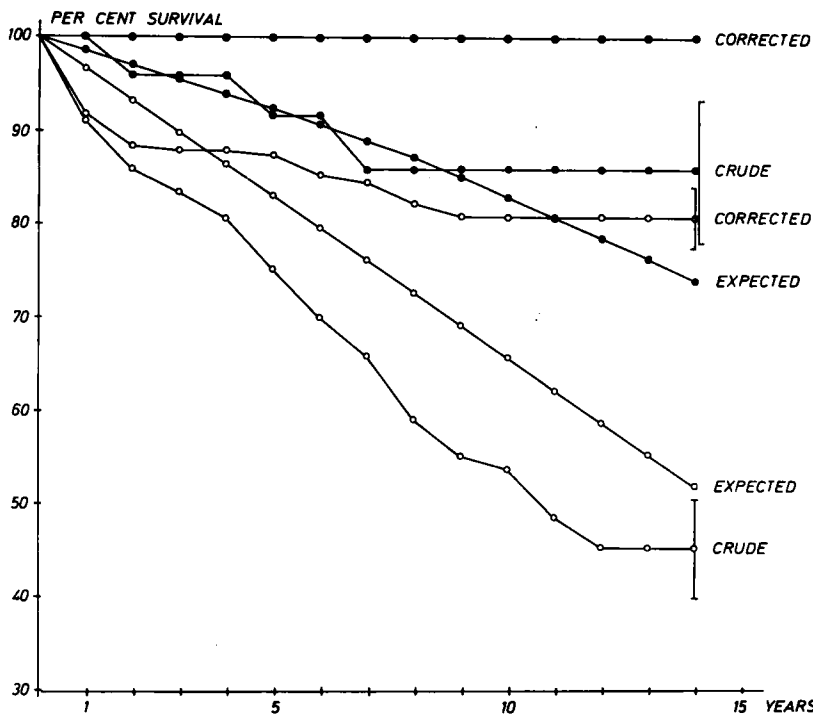


Fig. 5. Survival curves for 25 females (●) and 211 males (○) with glottic carcinoma. Standard error is marked in the curves.

total laryngectomy in the total series was 26 per cent (93/359) and did not change with increasing years of observation. The prognosis after total laryngectomy is rather good, the chance of cure being more than 50 per cent. Table 7 shows in what stages the secondary laryngectomies were performed.

Complications to irradiation. Practically all patients had moderate mucositis of the larynx during and shortly after the irradiation. Tracheostomy was performed in 12 patients before the irradiation because of respiratory obstruction, and during the treatment in 4 patients because of severe reaction with oedema. Painful reactions, perichondritis, developed in 9 patients; in 3 of these tracheostomy was carried out and in 2 total laryngectomies. Further details on complications will be given in a forthcoming report (HJELM-HANSEN et coll. 1979).

Complications after operation. Pharyngo-cutaneous fistulas after total laryngectomy developed in 17 per cent (16/93) of the patients; 12 healed after conservative treatment with a gastric tube, 10 within 2 months and the remaining 2 after one year. The fistulas were closed by operation in 4 patients 7 to 24 months after the total laryngectomy.

Prognosis and sex (Figs 5, 6). It is apparent that the difference between the sexes as to prognosis observed among supraglottic cases was not statistically significant.

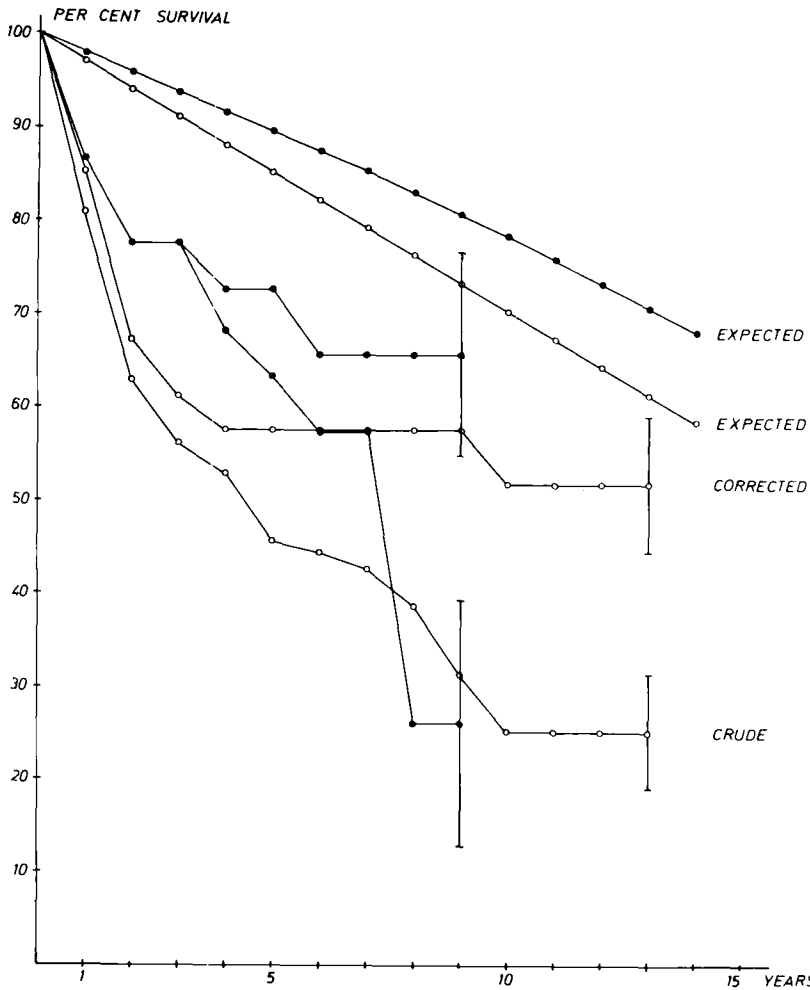


Fig. 6. Survival curves for 22 females (●) and 89 males (○) with supraglottic carcinoma. Standard error is marked in the curves.

In the glottic group a marked and clearly statistically significant difference could be observed, the female having a surprisingly better prognosis. Local recurrences occurred only in 2 of 25 females, which were cured by partial laryngectomy. It must be pointed out that females and males were fully comparable as to stage of disease and primary treatment.

Discussion

The incidence of carcinoma of the larynx has increased threefold in Denmark during the past 30 years (Fig. 1). The incidence for females is much lower than for males. CLEMMESSEN (1965) has shown that the incidence of the disease is increasing significantly with increasing age. The population of Denmark has changed from the

beginning of the registrations in 1943 to the last notifications in 1972, the older groups being represented to a higher degree during the last years. This change can undoubtedly explain some of the increase, but other factors also must be considered, i.e., the drift from rural to urban areas, the incidence in urban districts being 3 to 4 times higher than in rural districts.

No change could be observed in the appearance of the disease as regards age, histology, symptoms and signs, and stage of disease from the period 1963 to 1968, to that for 1968 to 1972, except for a change in sex rate, the female rate increasing from 10 to 15 per cent.

The central tumour dose was raised to 60 Gy in 1970, and the field technique changed. A fall in recurrence rate could be traced and this important finding was analysed separately and will be published later (HJELM-HANSEN *et coll.* 1979).

The treatment result from the first part of the period estimated from the crude survival rate (Fig. 3) did not change from the first to the last part of the period. However, the corrected survival curve was placed at a slightly higher level, indicating a higher cure rate. The frequency of total laryngectomy (Table 6) was unchanged, about 25 per cent throughout the period of observation. However, the surgical activity in case of local recurrence was higher in the period after 1970. The level of complications both after radiation therapy and secondary surgery was low throughout the entire period.

The policy of treatment whether to use primary irradiation or primary surgery is still an emotionally debated subject and the publications and discussions on the centennial conference on carcinoma of the larynx in Toronto (1974) give clear evidence of this. In the present report, that discussion will not be recapitulated. It will only be emphasized that in our opinion no reasons for abandoning primary irradiation have appeared.

The well-known fact (LEDERMAN 1961, ORMEROD 1964, HARRISON 1971, HANSEN 1975), that a clearly significant difference of prognosis exists between female and male among glottic cases (Fig. 5) is interesting and seems important. No explanation has been found. The material has been analysed with respect to age distribution, stage of disease, primary treatment and dose distribution, but the only finding was that the females have the debut of the disease earlier than males (Table 1), i.e., the sexes can be considered comparable. Another possible explanation could be a histologic one, the female carcinomas being less malignant. Histologic grading has been performed (LUND *et coll.* 1979) but revealed no differences between the two sexes. If this interesting problem can be solved, new therapeutic aspects might be revealed.

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SUMMARY

A series of 359 patients with carcinoma of the larynx was found to be very close to being representative of the northern part of Jutland, Denmark (north of Kongeåen). No unequivocal

cal change in the disease as regards sex, age, histology, symptoms and signs, and stage of disease could be observed during the period 1963 to 1972. A not statistically significant improvement in the corrected mortality appeared. The level of complications after irradiation and secondary surgery was found to be low. A statistically significant, better prognosis was found for females than for males in the glottic group.

ZUSAMMENFASSUNG

Eine Serie von 359 Patienten mit Larynxkarzinomen wurde als nahe zu vollständig repräsentativ für den nördlichen Teil von Jutland, Dänemark (nördlich von Kongeåen) befunden. Keine unzweideutige Änderung in der Erkrankung hinsichtlich Geschlecht, Alter, Histologie, Symptomen und Zeichen und Stadien der Erkrankung wurde während der Beobachtungsperiode zwischen 1963 und 1972 gefunden. Eine nicht statistisch signifikante Verbesserung in der korrigierten Mortalität wurde festgestellt. Das Niveau von Komplikationen nach Bestrahlung und sekundäre Operation wurde als niedrig befunden. Eine statistisch signifikant bessere Prognose wurde bei Frauen gegenüber Männern in der Gruppe mit Glottiskarzinomen gefunden.

RÉSUMÉ

Les auteurs ont constaté qu'une série de 359 patients atteints de carcinome du larynx était à très peu de chose près représentative de la partie septentrionale du Jutland, Danemark (au nord de Kongeåen). De 1963 à 1972 ils n'ont pas constaté de modification incontestable de cette maladie en ce qui concerne le sexe, l'âge, l'histologie, les signes fonctionnels et les signes cliniques et le stade de la maladie. Ils ont constaté une amélioration de la mortalité corrigée, mais elle n'est pas statistiquement significative. Le taux des complications après irradiation et après chirurgie secondaire a été faible. Ils ont constaté un meilleur pronostic statistiquement significatif pour les femmes par rapport aux hommes dans le groupe des carcinomes glottiques.

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