

FROM THE EAR, NOSE AND THROAT DEPARTMENT AND THE RADIUM CENTRE, UNIVERSITY HOSPITAL OF ODENSE, DK-5000 ODENSE, AND THE RADIUM CENTRE, UNIVERSITY HOSPITAL OF AARHUS, DK-8000 AARHUS, DENMARK.

CARCINOMA OF THE LARYNX

Series of 410 patients treated primarily with ^{60}Co irradiation

K. JØRGENSEN, J. MUNK, J. E. ANDERSEN and M. HJELM-HANSEN

Abstract

From 1965 to 1983 410 patients were treated for laryngeal carcinoma at the radium centre and the ENT department in Odense. No change in pattern of disease could be traced during the period of 18 years. The treatment was predominantly ^{60}Co irradiation with salvage surgery. 1977 to 1979 bleomycin, methotrexate and vincristine were given before irradiation. In 1979 split course radiation therapy was introduced in the treatment of stage II, III and IV cases and the patients were randomized, half of them receiving the radiosensitizer misonidazole, half of them placebo. Between 75 and 80 per cent of the patients were cured. Whereas chemotherapy did not change the survival some improvements may be traced in the period after 1979.

During the sixties treatment of head and neck tumours by supervoltage technique was introduced at most centres. From July 1965 to the January 1983, 410 new patients with laryngeal carcinoma were treated at the Radium centre and ENT department in Odense. The purpose of this communication is to present an analysis of these cases and the results of treatment. It is planned to select part of the series for further radiobiologic analysis and to publish the results in the near future.

Materials and Methods

All data from the records of the 410 patients were analysed by computer in the spring of 1983. Until October 1979 all data were gathered and put into our

computer retrospectively, but after that time as a planned prospective analysis.

As to general data the analysis includes all 410 cases. In order to have at least one year of observation the results of therapy include only cases primarily treated before January 1982, i.e. 374 cases.

Incidence. Fig. 1 a shows the incidence of laryngeal carcinoma in Denmark according to the publications from the Danish Cancer Registry (5-7, 15, 27). It is seen that both crude and age corrected incidences have been on the increase. However, it seems likely that a plateau has been reached since the middle of the sixties. The annual number of admitted patients to the centre in Odense has increased significantly during the period and the increase of incidence is illustrated in Fig. 1 b. We have observed an increase of nearly 400 per cent from the middle of the sixties to the period around 1980.

Histopathology. All cases with an uncertain histopathologic diagnosis were revised and a few cases were excluded because malignancy could not be established. Thus 410 cases remained, of which 409 had epidermoid carcinoma and one adenocarcinoma.

Sex ratio. The series comprised 40 females and 370 males, i.e. the ratio was 1:10. Among glottic cases 6 per cent (18/286) were females and among

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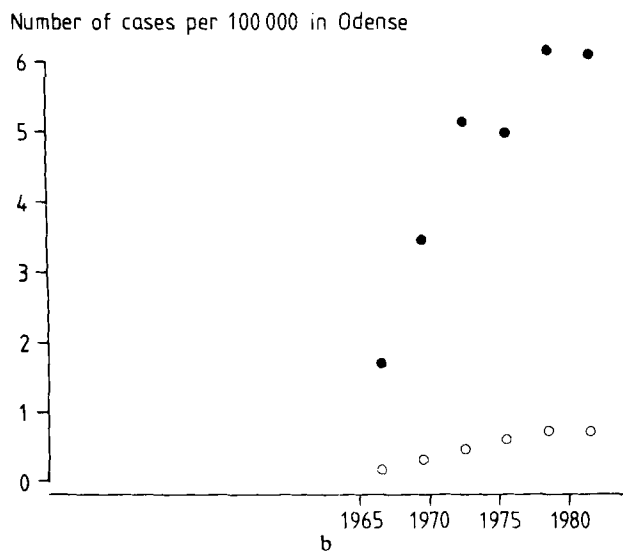
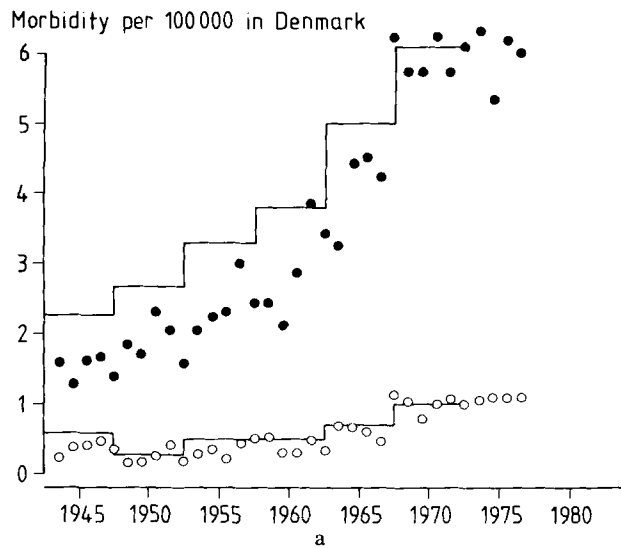


Fig. 1. a) Crude and age adjusted (for European standard population —) incidence of laryngeal carcinoma in Denmark 1943–1977. b) Crude incidence of laryngeal carcinoma in Odense 1965–1982. Average of 3-year periods. Males (●), females (○).

supraglottic cases 18 per cent (22/121). The three subglottic cases were all males.

Age distribution in cases with glottic and supraglottic locations is given in Fig. 2.

Symptoms and signs are given in Table 1. Hoarseness was the initial symptom in nearly all glottic cases, whereas only about half of the patients in the supraglottic group had hoarseness on admission.

Site of origin and TNM classification. The cases were classified according to the rules of UICC (32). Table 2 expresses the presumed site of origin of the tumour and Tables 3 and 4 give TNM classification and staging. Thirty-seven patients or 9 per cent (37/410) had lymph node metastases on admission,

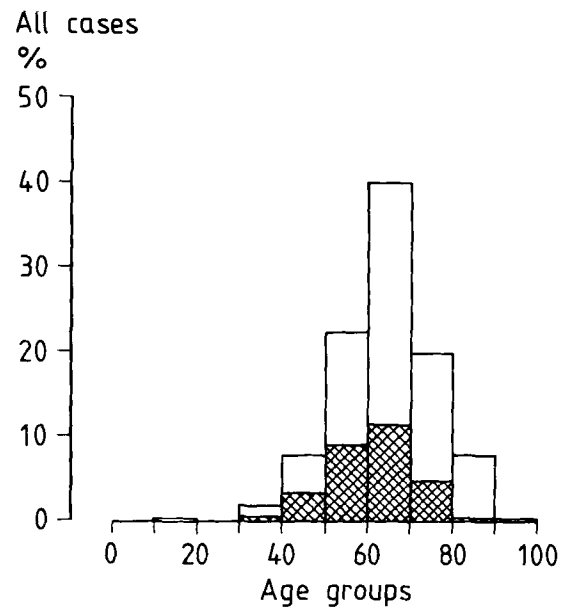


Fig. 2. Age distribution of patients with glottic (□) and supraglottic (▨) malignancies.

Table 1

Symptoms and signs in 410 patients treated 1965 to 1982

	Glottis	Supra-glottis	Sub-glottis	Total
No symptoms	3	1		4
Hoarseness	277	67	3	347
Irritation of the throat with pain	2	31		33
Otalgia		4		4
Dysphagia		4		4
Cough	1	4		5
Respiratory obstruction	2	3		5
Enlarged lymph nodes in the neck		5		5
Loss in weight		2		2
No information	1			1
Total	286	121	3	410

but only 4 cases were glottic. Hence the frequency in the supraglottic group was 27 per cent (33/121). The relationship between site and frequency of lymph node metastases is shown in Table 5. Higher location was related to larger frequency of lymph node metastases.

The policy of treatment changed during the period. Table 6 shows three periods of time and the corresponding policies. Table 7 lists the treatments actually given. From 1965 to 1977 the intention was to treat all cases with irradiation only. The source of

Table 2

Site of origin of tumours in 410 patients (per cent in parentheses)

Glottis	
Vocal cords	286 (100)
Supraglottis	
Epilarynx, posterior surface of	
suprahyoid epiglottis	25 (21)
Aryepiglottic fold	25 (21)
Arytenoid	3 (2)
Infrahyoid epiglottis	21 (17)
Ventricular cords	46 (38)
Ventricular cavities	1 (1)
Total	121 (100)
Subglottis	3

Table 3

TNM classification (32) of the tumours in 410 patients treated 1965 to 1982

	N0	N1	N2	N3	Total
Tis	30				30
T1a	114	1		1	116
T1b	30	3		1	34
T2	110	1		1	112
T3	55	5	1	3	64
T4	34	7	3	10	54
Total	373	17	4	16	410

irradiation was a ⁶⁰Co apparatus of kilocurie strength. A treatment shell was produced for each patient and simulator procedure was used to establish position and size of the fields. In glottic cases a field size of 6 cm × 6 cm was used most frequently. The fields were made larger in case of large tumours and in most supraglottic case to cover the regional lymph node regions. The technique was two opposing fields with both treated at each session. Compensating filters were applied in case of large fields, and the source skin distance was 85 cm. The central tumour dose was 57 Gy administered in 30 fractions during 6 weeks.

In the second period, from July 1977 to September 1979, our centre participated in a nationwide project DAHANCA I-BMV (Danish Head and Neck Cancer). Cases of stage 0, I and II received irradiation only whereas stage III and IV got bleomycin, methotrexate and vincristine before irradiation. The single doses were 13 mg/m² of bleomycin intramuscularly, methotrexate 20 mg/m² intravenously and vincristine 1 mg/m² intravenously. Table 8 shows the schedule of administration. The irradiation

Table 4

Stage of disease of 410 cases treated 1965 to 1982

	No. of cases	Per cent
Tis	30	7.3
Stage I	144	35.1
Stage II	110	26.8
Stage III	65	15.9
Stage IV	61	14.9
Total	410	100

Table 5

Relationship between site of primary tumour and frequency of lymph node metastases among supraglottic cases on admission (N-met. = lymph node metastases)

	No. of cases	No. with N-met.	Per cent
Epilarynx, posterior surface of suprahyoid epiglottis	25	10	40
Aryepiglottic fold	25	10	40
Arytenoid and infrahyoid epiglottis	24	6	25
Ventricular cords and cavities	47	7	15
Total	121	33	27

technique and fractionation were as described in the first period except that the central tumour dose was increased for all cases from 57 Gy to 60 Gy in the middle of the DAHANCA I period.

From October 1979 a new nationwide randomized project concerning the radiosensitizer misonidazole was initiated, DAHANCA II-misonidazole. All eligible patients with stage II, III and IV tumours were randomized, half of the patients receiving misonidazole (a total of 11 g/m²) during the first 4 weeks of irradiation and the remaining half of the patients receiving placebo. At the same time, split course irradiation with 2 schedules of fractionation were introduced for the randomized cases. The pattern of randomization is illustrated in Fig. 3. After 4 weeks of treatment a pause—split—was made lasting 3 weeks. The last part of radiation therapy—without drugs—was given as daily fractions in 2½ weeks regardless of initial fractionation. The central tumour dose in the two schemes was 66 to 68 Gy or 59 to 61 Gy at 5 or 2 fractions a week, respectively, the variations depending on the size of the treatment fields. The patients not randomized including stage

Table 6

Treatment policy of 374 patients (Chemother. = chemotherapy, Irr. = irradiation)

Period	March 1965 June 1977	July 1977 Sept. 1979	Oct. 1979 Dec. 1981
Name of period		DAHANCA I	DAHANCA II
Treatment policy			
Stage 0 and I	} Irradiation	} Irradiation	} Irradiation
Stage II			
Stage III and IV			

Table 7

Actual primary treatment of 374 patients

Actual treatment	Period		
	Before 1977	DAHANCA I	DAHANCA II
No treatment	1		
Stripping	2		
Partial laryngectomy	1		
Total laryngectomy	1	1	
Endoscopic extirpation + irradiation		1	
Irradiation only	222	49	42
Irradiation + chemotherapy	1		
Irradiation + chemotherapy + neck dissection	1		
Irradiation + total laryngectomy	1		
Irradiation + sensitizer/placebo			27
Chemotherapy + irradiation	2	22	
Total	232	73	69

Table 8

Schedule for treatment with cytostatic drugs (BLM = bleomycin, MTX = methotrexate, VCR = vincristine)

	Day			
	1	5	8	12
8 a.m.	VCR		VCR	
1 p.m.	BLM + MTX	BLM	BLM + MTX	BLM

0 and I were treated with radiation only and a daily fractionation was used to give 60 Gy, 30 fractions in 6 weeks.

Exceptions from the intended treatment (Table 6) occurred. The deviations from the policy are illustrated in Table 7. From a total of 368 patients receiving irradiation, 8 were unable to achieve at least 90 per cent of the prescribed tumour dose, and 9 patients were treated with a single anterior electron field instead of two cobalt fields. Three patients had other types of chemotherapy rather than BMV.

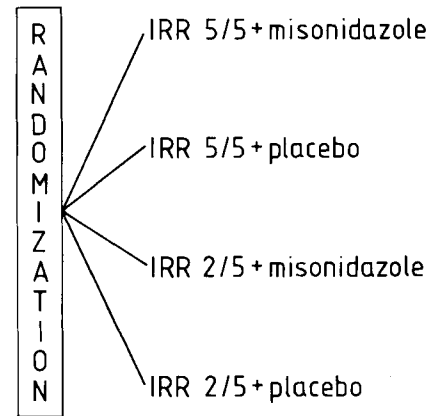


Fig. 3. Mode of randomization in the DAHANCA II project. IRR 5/5 or 2/5: irradiation 5 or 2 times a week.

Follow-up. All patients were followed up for between 1 and 17 years. However, clinical examinations ended after 10 years of observation.

If residual tumour was suspected at the end of radiation therapy or if the clinical examinations at

Table 9

Treatment intentions in 374 patients

	Curative treatment	Palliation or no treatment	Total	Recurrence-free after curative treatment
Primary treatment	371	3	374	240
First recurrence incl. residual tumours	96	35	131	62
Second recurrence	11	23	34	4
Third recurrence	1	6	7	1

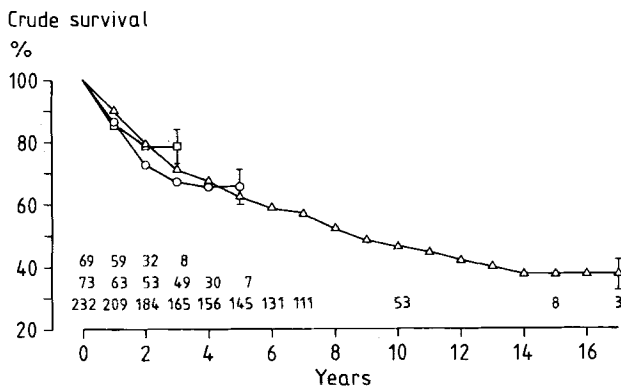


Fig. 4. Crude survival curves for 374 patients with laryngeal carcinoma. 1965-1977 (Δ). 1977-1979, DAHANCA I (○). 1979-1981, DAHANCA II (□).

Table 10

Type of surgery in 374 patients treated between 1965 and 1982

	Primary treatment	Supplementary treatment	Total
Stripping	2	-	2
Endoscopic extirpation	1	-	1
Fissure with cordectomy	-	1	1
Partial laryngectomy	1	16	17
Total laryngectomy	3	65	68
Total laryngectomy + neck dissection	-	8	8
Neck dissection	1	8	9
Local lymph node evacuation	-	2	2
Operation for stoma—recurrence	-	2	2
Total	8	102	110

follow-up were not satisfying, the patient was admitted for further examinations including direct laryngoscopy usually with biopsy. If residual tumour or recurrence was present, then the patient was treated by surgery (Table 10).

Pattern of disease. As demonstrated in Fig. 1 we have observed a significant increase of new cases during the period 1965 to 1983. We have investigated if there were any changes in the pattern of disease during the period. We have tested sex ratio, mean age at time of histologic diagnosis, TNM classification and duration of symptoms and signs as function of periods of three years and have observed no changes. We could observe no relationship between duration of symptoms and signs and stage of disease.

Results

The presentation of survival curves takes into account the different treatment policies in the three periods. All survival rates were calculated accord-

ing to the status of the patients per 1st of January 1983, and the files were checked against the Danish Civil Register as per 1st of June 1982 to reveal the state of survival. In case of death the cause was investigated, also for patients not longer in regular follow-up. The actuary method (31) was used and correction for mortality from causes other than laryngeal carcinoma was carried out by calculating the corrected mortality coefficients for the separate years of observation. Greenwoods formula was used for calculating the standard errors (31).

Figs 4 and 5a show crude and corrected survival curves for the whole series of 374 patients. The latter figure illustrates that between 75 and 80 per cent of all patients were cured of their disease, and there is some evidence of improvement during the DAHANCA II period. We have also produced expected and relative survival curves (relative survival = expected/crude), and the latter differ insignificantly from the corrected curves.

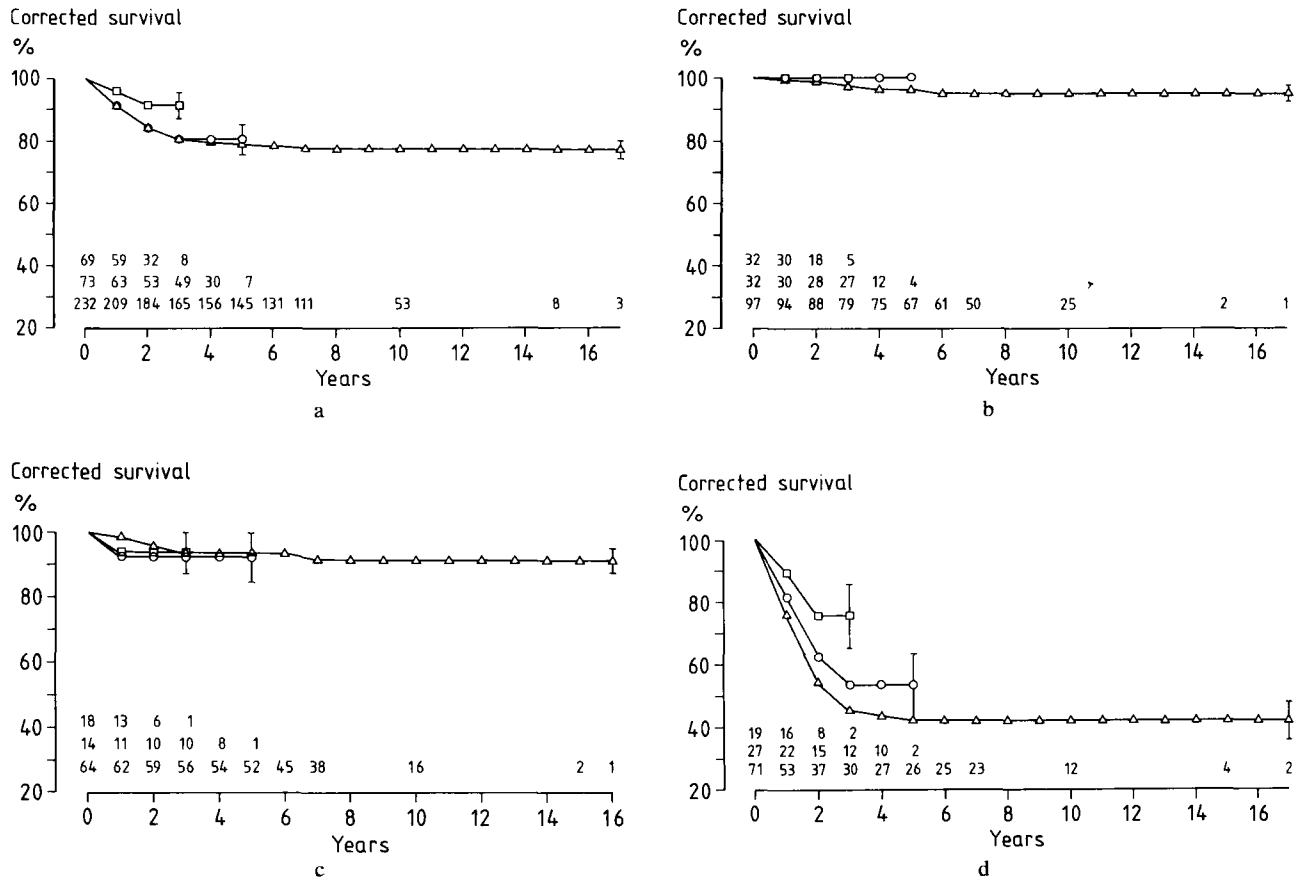


Fig. 5. Survival curves corrected for mortality other than laryngeal carcinoma. a) All stages (n=374). b) Stage 0 and I (n=161).

c) Stage II (n=96). d) Stage III and IV (n=117). Symbols as in Fig. 4.

Fig. 5 b indicates the situation concerning stage 0 and I and reveals that all cases have been cured since the beginning of the DAHANCA periods, i.e. after 30th of June 1977.

The 96 patients with stage II cancer (Fig. 5 c) were cured in more than 90 per cent of the cases in spite of quite a number of recurrences.

The survival curves (Fig. 5 d) of 117 patients with advanced carcinoma (stage III and IV) reveal quite a substantial difference between the early period of treatment and the DAHANCA II period. If the tendency of the DAHANCA II curve remains unchanged a further intake of patients will very likely show a statistically significant improvement.

As mentioned, nearly all patients had primary irradiation and recurrence free status after primary treatment is a good expression for the effect of treatment. It must be emphasized that the calculation includes all types of recurrences including persistent primary tumours. Fig. 6 a shows the probability of no recurrence after primary treatment of

all 374 patients; 371 received curative treatment and 240 have remained recurrence free as per 1st of January 1983 (see Table 9); 131 developed recurrences: 98 T, 7 N, 7 M, 15 TN, 2 TM, 1 TNM and 1 NM. The majority of recurrences appeared during the first two years of observation. The results indicate that recurrence is a rare event among Tis and stage I patients (Fig. 6 b) but not infrequent among stage II cases (Fig. 6 c). Comparison between Figs 6 c and 5 c illustrates the salvage achieved by supplementary surgery. Most of the patients in stages III and IV had residual tumour or recurrence after irradiation (Fig. 6 d).

Treatment of recurrences. Table 9 illustrates that 108 recurrences had curative treatment; 102 cases had surgery and 6 had irradiation with a curative aim. Table 10 lists the surgical activities in the series.

Frequency of total laryngectomy. During the period of observation 76 total laryngectomies were performed and hence the frequency of total laryngec-

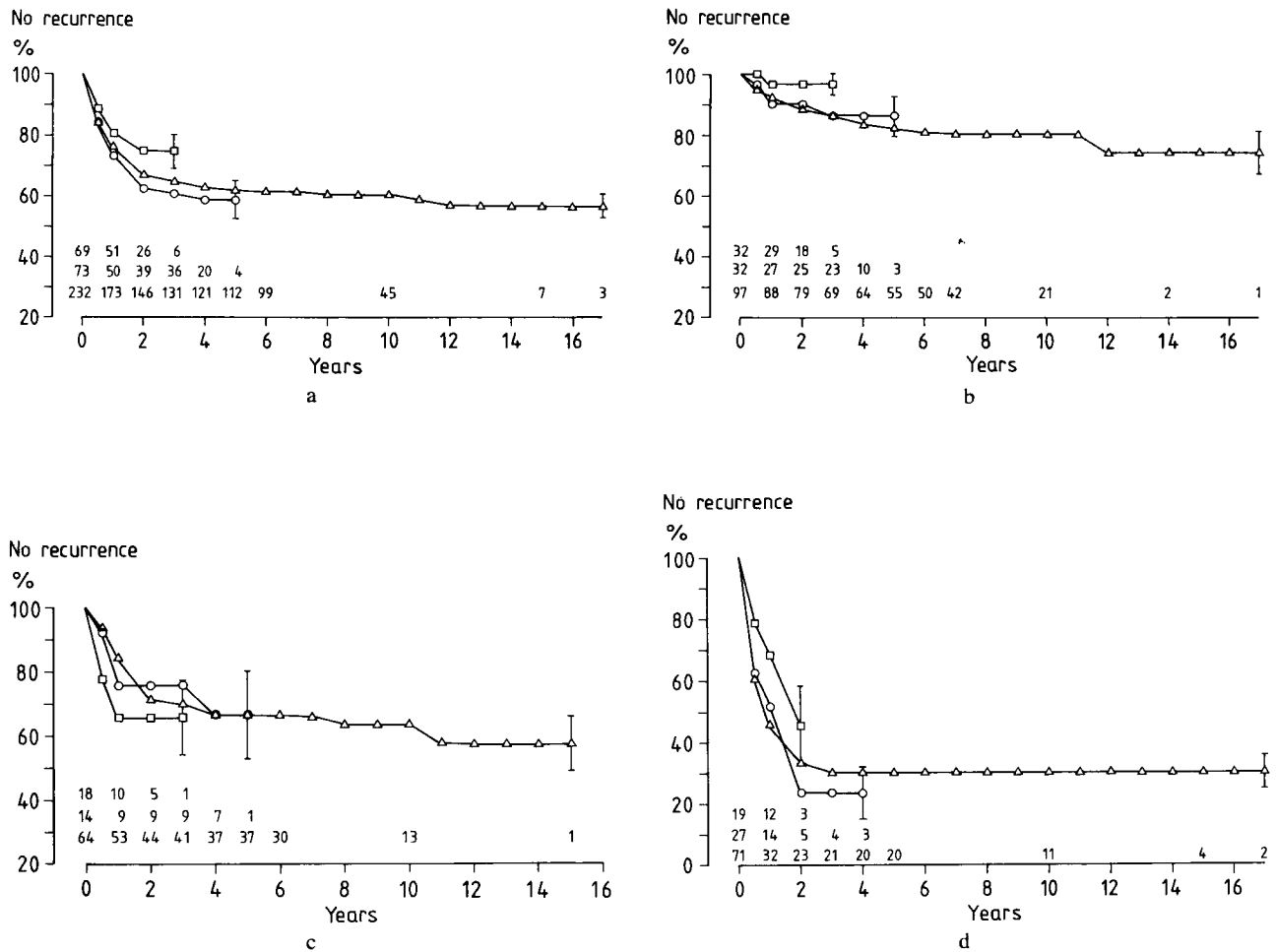


Fig. 6. Probability of no recurrence (T, N or M position) after primary treatment. a) All stages (n=374). b) Stage 0 and I

(n=161). c) Stage II (n=96). d) Stage III and IV (n=117). Symbols as in Fig. 4.

Table 11

Frequency of total laryngectomy as function of time of observation

Years of observation	No. of total laryngectomies (patients alive)	No. at risk	No. of total laryngectomies/No. at risk (per cent)
1	72	331	21.8
2	57	269	21.2
3	45	222	20.3
4	38	186	20.4
5	29	152	19.1
6	27	131	20.6
7	21	111	18.9
8	16	86	18.6
9	12	71	16.9
10	7	53	13.2
11	6	40	15.0

tomy in the total series is 20.3 per cent (76/374). In Table 11 the frequency of total laryngectomy of patients at risk is calculated and is found relatively unchanged during the period, being close to 20 per cent. Table 12 shows the primary stages in patients in whom total laryngectomy was performed.

Complications. All patients who received irradiation developed mucositis to some extent and a few showed severe reactions. After total laryngectomy 21 patients had pharyngocutaneous fistulas, i.e. 28 per cent (21/76). Before the DAHANCA periods the frequency of fistulas was 31 per cent (16/52) and afterwards it fell to 21 per cent (5/24). We have planned a publication of the radiobiologic effects of irradiation based on data from this series and therefore no further details are given here. During DAHANCA I and II periods we saw reactions from

chemotherapy and neuropathy from misonidazole but other nationwide publications in preparation will elucidate those problems.

Prognosis and sex. Whereas no significant difference could be observed in the supraglottic group, the prognosis was found statistically to be significantly better for females in the glottic group. In the supraglottic group 34 of 88 males and 4 of 18 females died from carcinoma. For glottic cases, the corresponding figures are 27 of 248 males and 0 of 17 females. The corrected 5-year survival after the life table method is given in Table 13.

Discussion

The incidence of carcinoma of the larynx has been increasing during the forties, fifties and sixties in Denmark as shown in Fig. 1. At the end of the sixties a plateau seems to have been reached. It is evident from the age adjusted curve of Fig. 1 that there was a real increase in incidence, not only caused by a change with domination of elderly people. The number of new cases admitted annually to the centre in Odense has increased remarkably also in the latest years, while the area of admission has remained constant. For some unknown reason the marked increase in incidence before the end of the sixties apparently has appeared with some delay in our area. In Norway and Sweden an increase similar to that in Denmark has been observed (4, 30). STELL (28) and BOYLE (2) have reported that the incidence in Great Britain is constant or even slightly decreasing.

The present series resembles other Danish series (9, 16, 17), as to sex rate, age distribution, histology, symptoms and signs and stage of disease. The first, however, contains more advanced cases. We have investigated whether any changes in disease pattern could be observed analysing of the series after splitting the time into periods of three years. We could not observe any change in sex ratio, mean age, TNM classification and duration of symptoms and signs. Hence, we find it justified to use the period before the DAHANCA projects as our own historical control. We expected to find a shorter duration of symptoms and signs and a change in dominance of earlier stages during the later years. During the period of 18 years no change could, however, be observed. We also found that advanced cases on an average did not have a longer duration of symptoms and signs than early ones, which might lead to the

Table 12

Stage of disease and frequency of laryngectomy among 374 patients. Three subglottic cases are excluded

	Glottis		Supraglottis	
	Per cent	No. of cases	Per cent	No. of cases
Stage 0-I	5	7/141	20	4/20
Stage II	20	16/79	38	6/16
Stage III	37	13/35	36	9/25
Stage IV	30	3/10	38	17/45

Table 13

Corrected 5-year survival rates

	Survival (per cent)
Glottis	
Males	88.1±2.2
Females	100.0±0.0
Supraglottis	
Males	58.5± 5.6
Females	76.3±10.4

rather depressing conclusion that earlier diagnosis will only slightly increase the proportion of early cases.

As already mentioned, the change of treatment principles gives some difficulties in reporting the results. The treatment results and complications of the DAHANCA I and II periods will not be commented in details here. Both projects are nationwide and the data from our series are pooled with results from the whole of Denmark (24). However, it is evident from Figs 4, 5 and 6 that the DAHANCA I period hardly changed the results whereas the DAHANCA II period with introduction of split course therapy and the radiosensitizer misonidazole may have improved the results. No definite conclusions can of course be drawn so far. Per 1st of September 1983, 480 patients have been randomized in Denmark. The trial is still going on and so far it has not been revealed if misonidazole influences the results.

The evaluation of the total therapeutic result must include the following factors: survival rates, frequency of total laryngectomy and complications after irradiation and supplementary surgery. We find that our treatment policy with primary irradiation affords an acceptable survival with a maximum preservation of laryngeal function. We regard this as

a main point and several authors emphasize the same points of view (3, 10, 11, 20, 29).

The concept of the 'best procedure' in the treatment of carcinoma of the larynx is still under debate. There are many supporters of primary surgery or mainly primary surgery (8, 14, 19, 21, 25, 26). These series show survival results of the same level or a little higher than ours, but naturally the frequencies of total laryngectomy are higher, twice as high or more.

Recently, BOCCA et coll. (1) published results from a large series of supraglottic carcinomas treated with primary surgery. The 5-year results are undoubtedly superior to those after irradiation alone.

In the present series, 161 patients had stage 0 or I carcinomas. As can be seen from Fig. 5b all patients, who received their first treatment after the beginning of the DAHANCA periods (i.e. medio 1977) were cured and the frequency of total laryngectomies among glottic stage I cases was only 5 per cent (see Table 12). As already mentioned stage 0 and I cases were not included in any of the DAHANCA projects. The reason why the results have improved is probably the increase in the dose of irradiation in the middle of 1978, from 57 to 60 Gy. We have previously made a similar encouraging observation at another treatment centre (13). Most authors agree that primary irradiation provides the best results in early stages of laryngeal carcinoma. Furthermore primary irradiation is cheaper than surgery (23).

As to stage II cases, 40 per cent in our series (Fig. 6c) developed recurrences, but after supplementary surgery more than 90 per cent were cured. Therefore we find no need for any change of treatment in this group of patients.

During recent years many authors have supported the idea of treating early cases with primary irradiation and advanced cases with planned combined therapy, i.e. preoperative irradiation and surgery (12, 18, 22, 33). It cannot be denied that the recurrence rate was unacceptably high in stage III and IV cases in our series. These observations have resulted in the randomized investigation of the effect of the radiosensitizer misonidazole and introduction of split course irradiation.

We have observed a non-statistically significant improvement in stage III and IV cases (Fig. 5d), and it is our hope that analysis of the DAHANCA II results in a year or two will determine whether the

improvement—if any—is caused by the introduction of split course irradiation or the radiosensitizer misonidazole.

In our series additional patient data have been gathered and investigations concerning the relationship between the radiobiologic effect of irradiation and recurrences as well as levels of complications are at present being performed and will be published in the near future.

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Request for reprints: Dr Karsten Jørgensen, Ear, Nose and Throat Department, Odense Sygehus, Sdr. Boulevard, DK-5000 Odense C, Denmark.

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