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ADVANCED SQUAMOUS CELL CARCINOMA OF THE LARYNX

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Abstract

Out of 676 patients with advanced squamous cell carcinoma of the larynx in stage III or IV, 673 patients received primary radiotherapy, either alone or in combination with surgery or chemotherapy. A significantly better survival with loco-regional control was obtained for women than for men. Also, the tumour size was of significant importance, as a better survival with loco-regional control was seen for tumours below 4 cm in largest diameter than for larger tumours. A similar advantage was seen as regards T1 and T2 tumours. There was no difference with regard to the patients' ages, tumour location, node status, or tumour stage III or IV. At 10 years, the crude survival for the total group of stage III and IV patients was 17%, corrected survival 38%.

Key words: Laryngeal cancer, advanced, squamous cell carcinoma, radiotherapy.

Primary radiotherapy has played an important role in the treatment of advanced laryngeal cancer throughout the years, and this has also been the case at the Department of Head and Neck Oncology at the Finsen Institute in Copenhagen.

We now present a retrospective analysis of the treatment results in advanced laryngeal carcinoma referred to our department in the period from 1965 to 1986.

Material and Methods

Patients. In this 22-year period, 1 926 patients with laryngeal carcinoma were referred to the Finsen Institute for treatment, and 676 (35%) of these patients had squamous cell carcinoma in stage III or IV (UICC 1978). The material included 126 females (19%) and 550 males (81%). The patients were aged 28 to 93 years (median age: 63) (Table 1).

Other tumour characteristics are shown in Table 2. Tumours in the supraglottic region were most frequent (70%), and the proportion of patients with this tumour location was higher in females than in males. Subglottic tumours were rare (3%). The tumour size mostly varied between 20 and 59 mm in largest diameter.

There were a few T1 and T2 tumours, but most patients had T3 (48%) and T4 (38%) tumours. At presentation, 62% of the patients had no palpable lymph node metastases (N0), while 22% were N1, 5% N2 and 11% N3. Distant metastases (M1) were found at presentation in 3%. In all, 52% of the patients had stage III and 48% stage IV disease.

All patients were primarily examined at a joint conference between radiotherapists and ENT-surgeons. The tumour was staged according to the TNM-classification (UICC 1978), and a treatment plan was worked out for each patient.

Radiotherapy. Radiotherapy by cobalt-60 beam or 4 MV x-rays from a linear accelerator was given to two lateral opposed fields including the primary tumour with a minimum margin of 2 cm and the neck lymph node regions (mid-jugular and subdigastric). Any palpable neck lymph nodes were also included in a field with a margin of 2 cm. The policy concerning the treatment volume did not change essentially during the period of investigation.

Naturally the fractionation schedules changed somewhat during the years, under the influence of new ideas of optimizing the treatment (Table 3). The schedule most often used was 1.8 to 2.0 Gy, one fraction per day, 5 fractions per week, continuously up to a tumour dose of 62 to 67 Gy in 6–7 weeks (77%). Other schedules with 2, 3 or 6 fractions per week were used in a minority of patients and with tumour doses supposed to produce a radiobiological effect similar to that of the routine schedule (1).

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Table 1

Age distribution

Age in years:	Women		Men	
	n	(%)	n	(%)
20–29			1	(–)
30–39	2	(2)	6	(1)
40–49	13	(10)	41	(7)
50–59	32	(25)	149	(27)
60–69	47	(37)	209	(38)
70–79	24	(19)	120	(22)
80–89	8	(6)	21	(4)
90–99	–	–	3	(1)
Total	126	(100)	550	(100)

Table 2

Patient and tumour characteristics

	Women		Men	
	n	(%)	n	(%)
Number of patients	126	(19)	550	(81)
Supraglottic	107	(85)	366	(67)
Glottic	18	(14)	166	(30)
Subglottic	1	(1)	18	(3)
Tumour size				
10–19 mm	4	(3)	9	(2)
20–29 mm	12	(9)	43	(8)
30–39 mm	36	(29)	179	(33)
40–49 mm	36	(29)	152	(28)
50–59 mm	28	(22)	107	(19)
60 mm	10	(8)	60	(11)
T1	14	(11)	34	(6)
T2	8	(6)	36	(6)
T3	48	(38)	280	(51)
T4	56	(44)	200	(36)
N0	72	(57)	349	(63)
N1	30	(24)	116	(21)
N2	9	(7)	22	(4)
N3	15	(12)	63	(11)
M0	122	(97)	535	(97)
M1	4	(3)	15	(3)
Stage III	57	(45)	292	(53)
Stage IV	69	(55)	258	(47)

Table 3

Treatment schedules in radiotherapy

	Number of Patients	(%)
5 fractions/week	520	(77)
6 fractions/week	21	(3)
3 fractions/week	11	(2)
2 fractions/week	6	(1)
Split-course irr. 2/5	55	(8)
Split-course irr. 5/5	59	(9)
Other	1	–

Table 4

Primary treatment

	Women		Men	
	n	(%)	n	(%)
Radiotherapy alone	103	(82)	445	(81)
Radiotherapy + surgery	1	(1)	14	(2)
Radiotherapy + chemotherapy	20	(15)	90	(17)
Surgery	0		1	–
Chemotherapy	2	(2)	0	–

During a certain period, split-course radiotherapy was given in accordance with the DAHANCA-2 project (2). In this project two different schedules were used, either 2 fractions of 4.13 Gy per week or 5 fractions of 2.0 Gy per week for 4 weeks, then a 3-week pause followed by another 5 fractions (2.0 Gy) a week for $2\frac{1}{2}$ week (total dose 59 Gy and 66 Gy respectively). These split-course schedules were used in 17% of our patients.

Combination treatment. Most of the patients were treated with radiotherapy alone (81%) (Table 4), but 2% of the patients received a planned combination of surgery and radiotherapy. All these patients had subglottic tumours and were treated from 1965 to 1972.

Sixteen per cent of our patients received chemotherapy in combination with radiotherapy either before or during radiotherapy. Bleomycin was the drug of choice for one period (3). A few of the patients who participated in the DAHANCA-1 project (4) were treated with vincristine, methotrexate and bleomycin.

One patient had surgery only and 2 patients chemotherapy only as palliative treatment for very advanced disease with distant metastases.

Results

The treatment results were estimated as actuarial survival with loco-regional control, and differences between survival were analysed by the log rank test (5).

As seen in Fig. 1, survival with loco-regional control was better for women than for men ($p = 0.004$), 44% versus 28% at 5 years, and 44% versus 24% at 10 years. There were no significant age-related differences.

The tumour location bore no significant relation to the outcome ($p = 0.48$) (Fig. 2). However, tumour size was important, and survival with loco-regional control was significantly better for tumours with a largest diameter below 40 mm than for the larger tumours ($p = 0.005$) (Fig. 3). There were also significant differences relating to T category ($p = 0.015$), (Fig. 4), but no apparent differences relating to N category. Stage III and stage IV were not significantly different concerning survival with loco-regional control ($p = 0.15$) (Fig. 5). The crude and relative survival curves for all 676 patients are shown in Fig. 6.

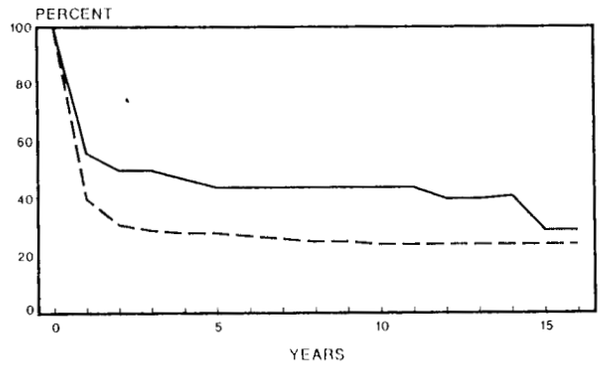

Fig. 1. Actuarial survival with loco-regional control according to sex. Female (———) and male (— — —)

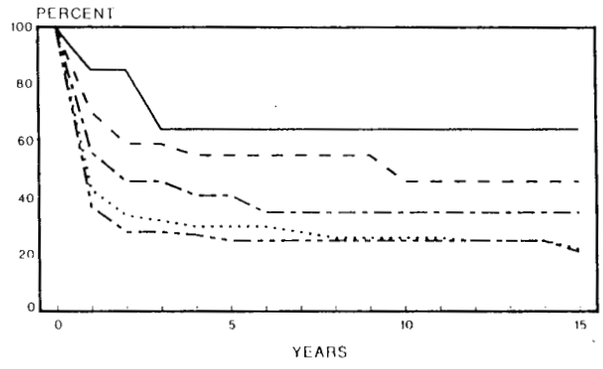

Fig. 4. Actuarial survival with loco-regional control according to T category. T1a (———), T1b (— · —), T2 (— — —), T3 (· · · · · ·) and T4 (— · · —).

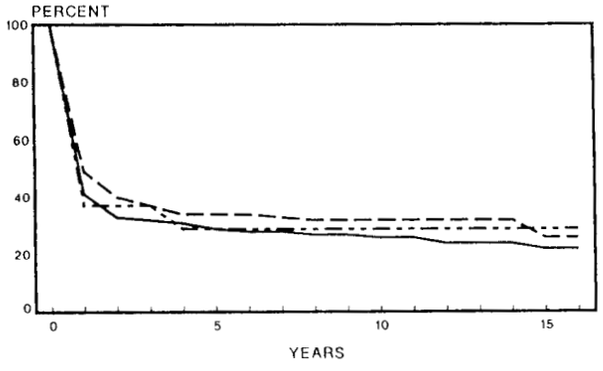

Fig. 2. Actuarial survival with loco-regional control according to primary tumour location. Supraglottic (———), glottic (— — —) and subglottic (— · · —).

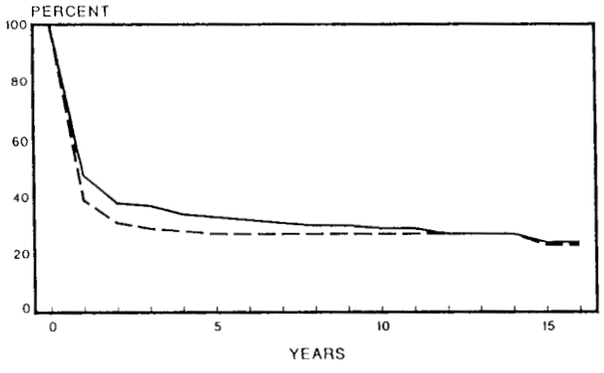

Fig. 5. Actuarial survival with loco-regional control according to stage. Stage III (———) and stage IV (— — —).

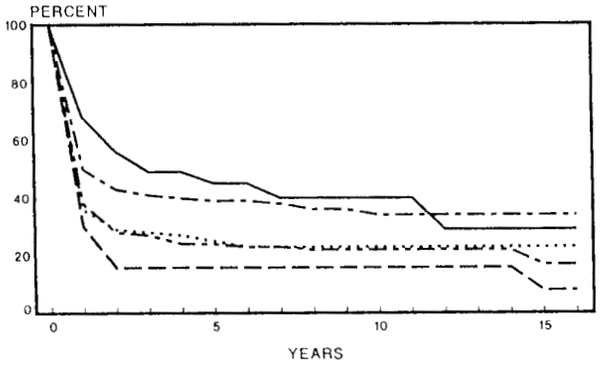

Fig. 3. Actuarial survival with loco-regional control according to primary tumour size. 20–29 mm (———), 30–39 mm (— · —), 40–49 mm (— · · —), 50–59 mm (· · · · · ·) and above 60 mm (— — —).

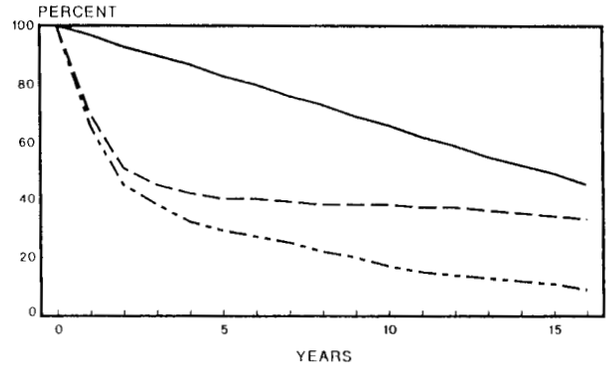

Fig. 6. Actuarial survival for all 676 patients. Crude survival (— · · —), relative survival (— — —), and survival in general population standardized according to sex and age (———).

The 5-year survival was 29% and 40% and the 10-year survival 17% and 38% respectively.

Discussion

During this 22-year period, radiotherapy played a major role in the treatment of advanced squamous cell carcinoma of the larynx, but several different attempts were made to improve the treatment for this serious disease. However, an analysis of the material according to different treatment schedules of radiotherapy or of simultaneous surgery or chemotherapy showed no obvious benefit from any of these attempts. Some of our patients participated in the Danish Head and Neck Cancer Studies (DAHANCA), and the results of these studies have now been published (2, 4, and unpublished data by Overgaard et al., 1989). A prospective, randomized trial evaluating the hypoxic radiosensitizer misonidazole (2) showed a tendency towards improved loco-regional control for male patients with supraglottic cancer, but this was not significant, and no advantage was observed for patients with glottic cancer. In the same study, two different radiotherapy schedules were examined, 2 fractions per week versus 5 fractions per week, but no difference was found (2). Chemotherapy (bleomycin, methotrexate, and vincristine), given before radiotherapy to patients with laryngeal carcinoma stage III and IV, failed to improve the patient's survival (4).

Thus, no convincing improvement in the treatment of advanced laryngeal squamous cell carcinoma has so far been shown in our department.

Patients with supraglottic laryngeal carcinoma are at present allocated to a new prospective, randomized trial of another radiosensitizer (nimorazole), and a radiotherapy schedule of continuous treatment (2 Gy per fraction, 5 fractions per week to 62–68 Gy (DAHANCA-5)). An interim report from this trial has shown a better total survival compared to the earlier trial with split-course therapy, probably related to the change in treatment schedule (6). However, this trial is still on-going and no definite results can yet be reported.

Another possibility of improving the treatment results may be accelerated fractionation of radiotherapy, as described by Wang (7, 8). As regards patients with advanced laryngeal squamous cell carcinoma a Scandinavian multicentre trial is now being planned.

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