ORIGINAL ARTICLE

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Laryngeal Carcinoma

Multivariate Analysis of Prognostic Factors in 1 252 Consecutive Patients Treated with Primary Radiotherapy

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Acta Oncologica Vol. 42, No. 7, pp. 771–778, 2003

Multivariate analyses of prognostic factors were carried out in 1 252 consecutive patients with laryngeal squamous cell carcinoma treated with primary radical radiotherapy. Ten percent of patients had positive neck nodes. Most of the patients were in stage I (48%), the remainder in stage II (24%), III (18%) and IV (10%). Of these patients, 746/1 252 (60%) were controlled by primary treatment but 506/1 252 (40%) had residual tumor or recurrent disease. The larynx was preserved in 62% of patients. The 5-year actuarial values for disease-specific and overall survival were 78% and 60%, respectively. The results of a univariate analysis showed multiple significant prognostic factors, and in a Cox proportional hazards model it was found that gender and T-classification were significant for T-failure, locoregional failure, death from cancer and death from all causes. The region of origin, nodal involvement, differentiation and pretreatment hemoglobin value were significant for several of the above-mentioned endpoints. Laryngeal carcinoma is curable when treated with primary radiotherapy, and this treatment confers a high degree of organ preservation. Independent prognostic factors in the multivariate analyses were gender, region of origin, T-stage, nodal involvement, differentiation and hemoglobin.

Received 22 April 2003
Accepted 15 August 2003

The main goal of this series of 1 252 patients with laryngeal carcinoma was to present a multivariate analysis of the prognostic parameters. In two previous publications on supraglottic carcinoma (1) and glottic carcinoma (2) we described the primary treatment and recurrence pattern of laryngeal carcinoma in one institution. The incidence of laryngeal cancer in Denmark is among the lowest reported in the European countries, but from 1975 to 1998 there has been an increase in the annual incidence from 183 to 247 (3, 4). During the past 10 years the incidence of newly diagnosed cases has been stable, with an average of 210 males and 45 females per year. In Denmark one-third of tumors of the larynx originate from the supraglottic area and two-thirds from the glottic area.

The optimal primary treatment strategy for laryngeal cancer is still a subject of international debate. During the period reported, the treatment policy in Denmark has been that all patients should be considered for primary radiotherapy in order to preserve the larynx in as many as possible. This treatment policy is an established tradition and has been described in two theses (5, 6). Since the end of the period covered by this study, the standard treatment has been intensified and includes hypoxic cell sensitizers and accelerated radiotherapy.

The aim of this study was to demonstrate prognostic factors in a multivariate analysis. The subjects were consecutive, non-selected patients with squamous cell carcinoma of the larynx. All the patients were treated with primary radiotherapy with curative intent and there was no referral bias.

MATERIAL AND METHODS

The original material included 1 298 consecutive patients with laryngeal carcinoma referred to the head and neck oncology team at Aarhus University Hospital from January 1963 to December 1991. The institution receives all patients from an area with approximately 1 million inhabitants. The present analysis concerns all patients, 1 252/1 298 (96%), in whom the treatment was primary radiotherapy with curative intent (27 patients did not have treatment with curative intent and, for various reasons, 19 had primary, curatively intended surgery). Before the start of treatment, both a specialist in oncology and an ENT specialist assessed the

 ISSN 0284-186X
DOI: 10.1080/02841860310017595

Table 1

Tumor origin in larynx (UICC 1982)

SUPRAGLOTTIC	
Epilarynx	
Posterior surface of suprahyoid epiglottis	70 (6%)
Aryepiglottic fold	43 (3%)
Arytenoid	20 (2%)
Supraglottic excluding epilarynx	
Infrahyoid epiglottis	93 (7%)
Ventricular bands (false cords)	166 (13%)
Ventricular cavities	4 (0.3%)
GLOTTIC	
Vocal cords	811 (65%)
Anterior commissure	23 (2%)
Posterior commissure	0
SUBGLOTTIC	22 (2%)
TOTAL	1 252 (100%)

patients, including assessment and a biopsy under general anesthetic.

One hundred and seventy-three (14%) of the patients were females and 1 079 (86%) were males, median age 64 years (range 18–90 years). All the patients had biopsy-proven squamous cell carcinoma. The histological grading was recorded in 1 168/1 252 (93%) tumors; 481 (41%) were well differentiated, 392 (34%) moderately and 295 (25%) poorly differentiated. A modified Jakobsson scoring system (7) was also applied in 995 patients. Eight parameters were analyzed, four relating to the tumor cell, and four to the tumor–host relationship. Most of the tumors, 811/1 252 (65%), originated from the vocal cords; the involved regions and sites of origin are listed in Table 1. A small proportion, 123/1 252 (10%), of the patients had metastatic lymph nodes at presentation, the most frequently involved nodes being the homolateral subdigastric and mid-jugular nodes. All tumors were classified or re-classified according to the UICC 1982 classification (8) and the distribution is presented in Table 2. The majority of the patients were in stage I (48%) or II disease (24%) while fewer patients were in stage III (18%) or IV (10%) disease. The standard radical radiotherapy technique was parallel opposing lateral fields using cobolt-60 in 1 016 patients (81%) or 4–6 MV photons in 236 patients (19%). The primary target included the tumor and any involved lymph nodes. The different treatment schedules are listed in Table 3. To compensate for variations in the biological effect of different fractionation schedules, the actual delivered total radiation dose was recalculated as the biological equivalent given in 2 Gy fractions using an α/β ratio of 10 Gy for tumor response. In the last part of the period, prophylactic neck irradiation of clinically non-involved regions on the neck to a dose of 46–50 Gy was applied for T3–T4 tumors using a shrinking field technique. The spinal cord was shielded at the same dose, and the posterior neck (if involved) was treated to the high dose with electrons. Fifty-six patients received a hypoxic cell radiosensitizer, either misonidazole or nimorazole, as a part of the randomized trials DAHANCA 2 (9) and DAHANCA 5 (10). Eleven patients were included in the DAHANCA 1 study of induction chemotherapy with administration of bleomycin, methotrexate and vincristine (11).

A team of specialists in ENT and oncology followed the patients at regular intervals for a period of five years after treatment. The follow-up status was routinely documented, and all charts were reviewed for the present analysis. All the patient data were updated per September 1, 2000 using the Central Population Registry to check vital status. The data were recorded in a Medlog® database and SPSS® computer software was used in the analysis. The endpoints were: 'T control' or 'T-failure'—local control or failure in the primary site, and 'primary locoregional control' or 'primary locoregional failure'—combined primary tumor and nodal control or failure. In 'disease-specific survival' or 'death from carcinoma' the event was death from or with the cancer in question, and in 'overall survival' or 'death from all causes' the event was death from all causes. The Kaplan–Meier estimates were compared using a log-rank test with a significance level of 1% to reduce any problems with mass significance. The independent significant parameters from the univariate analysis were tested in a multivariate Cox proportional hazards model. Parameters were included in the model using forward selection, and the level of significance was selected as 5%.

Table 2

Stage distribution of 1 252 patients with laryngeal squamous cell carcinoma treated with primary radiotherapy (UICC 1982)

	N0	N1	N2	N3	Total
T1a	460	6	0	2	468 (37%)
T1b	146	8	4	1	159 (13%)
T2	304	11	1	3	319 (25%)
T3	165	29	6	12	212 (17%)
T4	54	22	8	10	94 (8%)
Total	1 129 (90%)	76 (6%)	19 (2%)	28 (2%)	1 252 (100%)

No patients with distant metastases.

Table 3

Treatment schedules for 1 252 patients receiving curative intended radiotherapy

Period	Cobalt No.	Lin. ac No.	No. patients in period	Treatment policy. If not otherwise mentioned: 5 fx/wk	No. treated insufficiently*	α/β eqivalent Gy
01.01.63–30.06.70	All		240	57 Gy/30 fx	17	56.5
01.07.70–31.12.77	All		330	60 Gy/30 fx	4	60
01.01.78–31.01.85	All		356			
			6		6	
			2	60–64 Gy/30–32 fx		60–64
			27	33.04 Gy/8 fx/4 wk–3 wk split–26–28 Gy/13–14 fx		65–67
			321	40 Gy/20 fx–3 wk split–26–32 Gy/13–16 fx		66–72
01.02.85–31.12.85	All		38	60 Gy/30 fx	0	60
01.01.86–31.12.91	52	236	288	62–66 Gy/31–33 fx	4	62–66

*Treated insufficiently if total dose was $\leq 90\%$ of this period's treatment policy.

RESULTS

The patients' course from diagnosis to either tumor control or failure is shown in Fig. 1. Primary treatment was effective in controlling 746/1 252 (60%), while 506/1 252 (40%) patients had persistent tumor or developed recurrent disease. Curatively intended recurrence treatment was offered to 370 patients; 364 patients were treated with surgery and 6 patients with radiotherapy. Recurrence treatment resulted in 224 patients being successfully salvaged, 16 of these after a second recurrence. Therefore the final result was that 970/1 252 (77%) patients were controlled for their laryngeal carcinoma. Of the cured patients, 170 had a total laryngectomy and 28 a partial laryngectomy; in other words larynx preservation was obtained in 772/1 252 patients corresponding to 62% of the patients. The patients treated with a total laryngectomy included 2 patients who had late edema without recurrence.

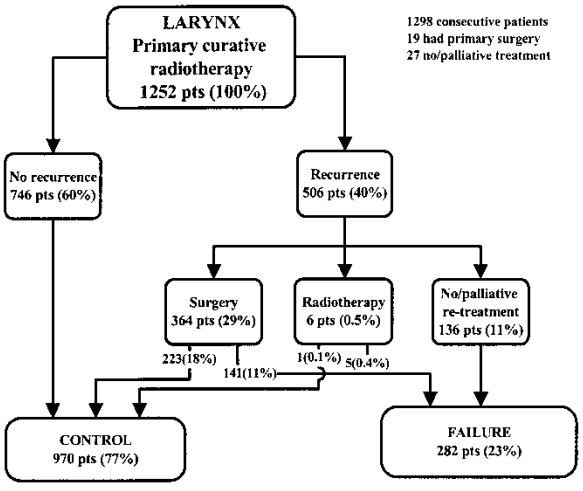


Fig. 1. Clinical course from diagnosis to tumor control or treatment failure in 1 252 patients with laryngeal carcinoma treated with primary radiotherapy.

Prognosis

The treatment outcomes for selected parameters for the 1 252 patients treated with radiotherapy are listed in Tables 4 and 5. The results are univariate Kaplan–Meier estimates with 5-year values for number of events and percentages. The results are listed for T control, primary locoregional control, disease-specific survival and overall survival. N control is not described as only around 10% had N-failure. Most events were seen within the first 2 years of observation. Patient gender had an influence on tumor control and overall survival, with the best prognosis observed for women. Survival parameters were influenced by age only. The region of origin was highly significant with the best prognosis seen for glottic tumors. T-classification, T-size, N-classification, tumor stage, differentiation and histological scoring system were significant for all endpoints. Pretreatment hemoglobin concentration, with cut-points dividing the material into four groups, shows a significantly poorer prognosis in the lowest quartile compared to the rest, as demonstrated in Fig. 2 for disease-specific survival.

Total delivered dose (in 2 Gy/fx equivalence) did not have any significant effect on the treatment results in this study. If patients treated with split-course radiotherapy and those insufficiently treated (Table 3) were excluded from the analysis, it could be demonstrated that a shorter treatment time (≤ 46 days) was more effective than prolonged treatments.

The treatment result over time was evaluated. A significant improvement in local and locoregional control, an unaltered disease-specific survival and a decreased overall survival is shown in Table 4 (treatment period). As can be seen in Fig. 3, the percentage of large tumors was higher in the first than in the last part of the period. To differentiate this finding, Table 5 is grouped into T1 to T4 tumors to analyze the subgroups. Small tumors were best controlled in the period with 60 Gy as standard treatment and larger tumors were best treated in the period with 66 Gy as the

Table 4

Univariate actuarial analysis of prognostic factors in 1252 patients with laryngeal squamous cell carcinoma treated with radiotherapy and curative intent. The listed events are 5-year values and the percentages are 5-year Kaplan–Meier estimates ±SE. Significant differences (1% level) are indicated in italic bold type

Parameter	No.	T control		Primary locoregional control		Disease-specific survival		Overall survival	
		Events	%	Events	%	Events	%	Events	%
All patients	1252	399	66±1	459	61±1	251	78±1	498	60±1
Female	173	***43***	***74±3***	***51***	***69±4***	24	85±3	***54***	***69±4***
Male	1079	***356***	***65±2***	***408***	***60±2***	227	77±1	***444***	***59±2***
Age 18–65	689	230	65±2	262	61±2	***122***	***82±2***	***202***	***71±2***
65+	563	169	67±2	197	62±2	***129***	***74±2***	***296***	***47±2***
Supraglottic	396	***166***	***55±3***	***208***	***44±3***	***137***	***63±3***	***206***	***48±3***
Glottic	834	***222***	***72±2***	***240***	***69±2***	***108***	***86±1***	***281***	***66±2***
Subglottic	22	***11***	***50±11***	***11***	***50±11***	***6***	***72±10***	***11***	***50±11***
T1a	468	***81***	***81±2***	***94***	***79±2***	***39***	***91±1***	***125***	***73±2***
T1b	159	***41***	***72±4***	***51***	***66±4***	***25***	***83±3***	***62***	***61±4***
T2	319	***116***	***61±3***	***129***	***57±3***	***55***	***81±2***	***124***	***61±3***
T3	212	***107***	***46±4***	***122***	***39±4***	***81***	***59±4***	***120***	***43±3***
T4	94	***54***	***38±6***	***63***	***28±5***	***51***	***41±5***	***67***	***29±5***
T-size 1–19 mm	248	***39***	***83±2***	***46***	***80±3***	***16***	***93±2***	***63***	***75±3***
T-size 20–29 mm	371	***92***	***73±2***	***103***	***70±2***	***48***	***86±2***	***124***	***67±2***
T-size 30–34 mm	369	***128***	***63±3***	***145***	***59±3***	***80***	***76±2***	***158***	***57±3***
T-size 35+ mm	263	***140***	***42±3***	***165***	***33±3***	***107***	***56±3***	***149***	***43±3***
N0	1129	***342***	***68±1***	***378***	***65±1***	***183***	***82±1***	***412***	***63±1***
N+	123	***57***	***50±5***	***81***	***29±4***	***68***	***41±5***	***86***	***30±4***
Stage I	606	***116***	***80±2***	***133***	***77±2***	***54***	***90±1***	***172***	***72±2***
Stage II	304	***110***	***61±3***	***120***	***58±3***	***49***	***82±2***	***115***	***62±3***
Stage III	219	***110***	***46±4***	***122***	***41±4***	***77***	***62±3***	***122***	***44±3***
Stage IV	123	***63***	***44±5***	***84***	***28±4***	***71***	***39±5***	***89***	***28±4***
Well differentiated	481	***101***	***77±2***	***110***	***76±2***	***51***	***88±2***	***145***	***70±2***
Mod. Differentiated	392	***129***	***65±3***	***150***	***59±3***	***69***	***81±2***	***158***	***60±2***
Poorly differentiated	295	***134***	***52±3***	***158***	***44±3***	***105***	***62±3***	***155***	***47±3***
Score 1.0–2.1	368	***77***	***77±2***	***91***	***73±2***	***33***	***90±2***	***114***	***69±2***
Score 2.2–2.5	323	***108***	***65±3***	***120***	***61±3***	***59***	***80±2***	***115***	***64±3***
Score 2.6+	304	***130***	***54±3***	***150***	***48±3***	***97***	***66±3***	***151***	***50±3***
High hemoglobin*	831	***259***	***67±2***	***296***	***63±2***	***148***	***81±1***	***306***	***63±2***
Low hemoglobin*	293	***110***	***59±3***	***131***	***52±3***	***91***	***66±3***	***160***	***46±3***
RT time[#] ≤46 days	643	***176***	***71±2***	***204***	***67±2***	***103***	***82±2***	236	63±2
47+ days	225	***82***	***61±3***	***92***	***57±3***	***56***	***73±3***	97	57±3
Treatment period									
63–70 (~57 Gy)	240	***96***	***59±3***	***107***	***55±3***	54	77±3	***80***	***67±3***
70–78+85 (~60 Gy)	368	***94***	***73±2***	***109***	***69±2***	61	82±2	***136***	***63±3***
78–85 (split course)	356	***122***	***63±3***	***144***	***56±3***	76	77±2	***148***	***58±3***
86–91 (~66 Gy)	288	***87***	***67±3***	***99***	***62±3***	60	77±3	***131***	***54±3***

*Cut point: 7.90 mmol/L for females and 8.56 mmol/L for males.
[#]Excl. split course and insufficiently treated patients (Table 3).

standard. It is demonstrated that the disease-specific survival was unaltered, but the overall survival for the patients dropped during the periods covered. We also checked other parameters of interest. In our four treatment periods the frequency of women increased from 11% to 17%. The proportion of supraglottic in relation to glottic tumors dropped from 33% to 30%. Evaluation of the differentiation showed that over time more patients had highly differentiated tumors, fewer had moderately differentiated tumors, while the proportion of poorly differentiated tumors was unaltered. The median radiation field sizes increased from 36 cm^2, over 42 and 42 to 49 cm^2 in the four periods. In the third and fourth periods 30 and 20 patients had a hypoxic radiosensitizer (all patients with tumors from T2 and larger), 27% and 25% died of a recurrence. Few patients in the second and third periods had induction chemotherapy (4 and 7 patients, respectively).

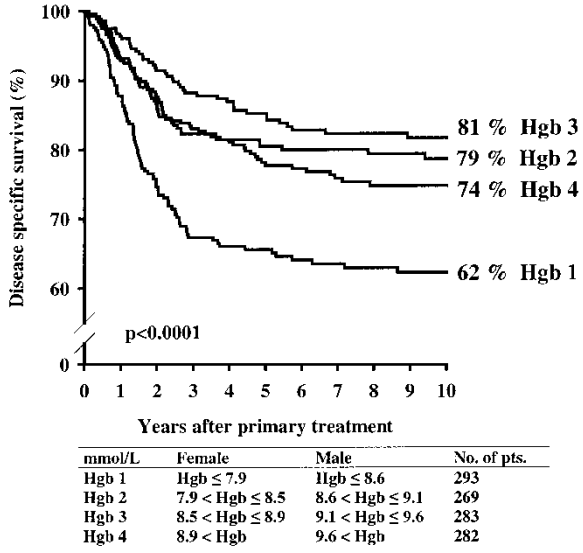
The material was analyzed using the Cox proportional hazards model for independent significant parameters for the endpoints T-failure, primary locoregional failure, death from cancer, and death from all causes (Table 6). The analysis included 1124 patients in whom all parameters were available. Gender and T-stages were significant for all

Table 5

Univariate actuarial analysis of classification versus treatment schedule and period in patients with laryngeal squamous cell carcinoma treated with radiotherapy and curative intent. The listed events are 5-year values and the percentages are 5-year Kaplan–Meier estimates ±SE. Significant differences (1% level) are indicated in italic bold type

	Parameter	No.	T control		Primary locoregional control		Disease-specific survival		Overall survival	
			Events	%	Events	%	Events	%	Events	%
	Treatment period									
T1	63–70 (~57 Gy)	101	23	77±4	***24***	***76±4***	8	92±3	15	85±4
	70–78+85(~60 Gy)	186	26	85±3	***28***	***83±3***	12	93±2	58	69±3
	78–85 (split course)	198	42	76±3	***54***	***70±3***	22	88±3	62	69±3
	86–91 (~66 Gy)	142	31	76±4	***38***	***71±4***	22	83±3	51	64±4
	Treatment period			7%		***<1%***		22%		5%
T2	63–70 (~57 Gy)	65	***31***	***52±6***	***36***	***45±6***	11	82±5	22	66±6
	70–78+85(~60 Gy)	97	***26***	***72±5***	***29***	***69±5***	17	83±4	31	68±5
	78–85 (split course)	80	***34***	***54±6***	***36***	***51±6***	11	84±4	30	63±5
	86–91 (~66 Gy)	77	***25***	***63±6***	***28***	***59±6***	17	74±6	40	48±6
	Treatment period			***<1%***		***<1%***		76%		10%
T3	63–70 (~57 Gy)	42	24	42±8	25	39±8	16	61±8	20	52±8
	70–78+85(~60 Gy)	59	27	53±7	32	45±7	21	61±7	31	47±7
	78–85 (split course)	60	34	32±8	41	23±7	30	47±7	39	33±6
	86–91 (~66 Gy)	51	22	52±8	24	48±8	14	70±7	28	44±7
	Treatment period			29%		9%		20%		39%
T4	63–70 (~57 Gy)	32	18	42±9	22	29±8	19	37±9	23	28±8
	70–78+85(~60 Gy)	26	15	37±10	19	22±9	12	51±10	16	38±10
	78–85 (split course)	18	12	33±11	13	25±11	13	23±11	16	11±7
	86–91 (~66 Gy)	18	10	43±13	9	43±13	7	56±13	12	33±11
				86%		60%		23%		21%

endpoints. The region of origin was significant for 'primary locoregional failure' and 'death from cancer', as the prognosis was best for the glottic patients. Nodal involvement was significant for all parameters except 'T-failure' and differentiation was significant for all parameters except 'death from all causes'. The pretreatment hemoglobin value was significant for 'death from cancer' and 'death from all causes'.



mmol/L	Female	Male	No. of pts.
Hgb 1	Hgb ≤ 7.9	Hgb ≤ 8.6	293
Hgb 2	7.9 < Hgb ≤ 8.5	8.6 < Hgb ≤ 9.1	269
Hgb 3	8.5 < Hgb ≤ 8.9	9.1 < Hgb ≤ 9.6	283
Hgb 4	8.9 < Hgb	9.6 < Hgb	282

Fig. 2. Disease-specific survival and hemoglobin in 1 127 patients.

DISCUSSION

The aim of the Danish treatment strategy using primary radiotherapy is to preserve laryngeal voice in as many as possible, saving patients from the morbidity of a primary laryngectomy, with surgery reserved for salvage in patients with recurrent disease. Based on our data presented here and earlier (1, 2) and other Danish results (12), the control rates of this strategy are comparable with other large studies

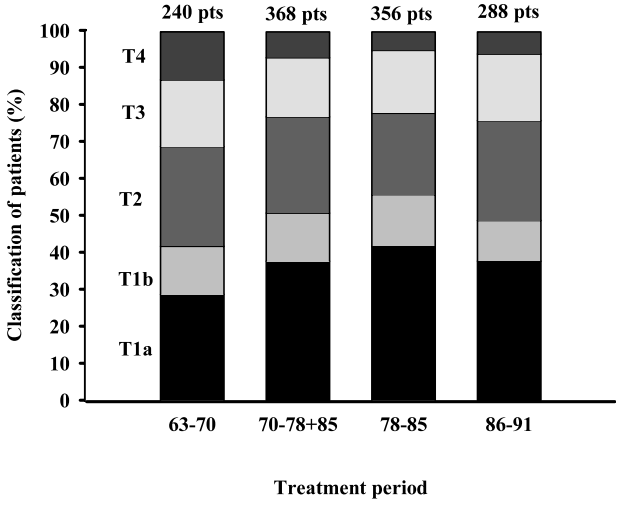


Fig. 3. Classification of the patients in relation to different treatment periods.

Table 6

Cox proportional hazard analysis of prognostic factors for treatment outcome in 1 252 patients with laryngeal squamous cell carcinoma treated with radical radiotherapy. The analysis included 1 124 patients for whom all listed parameters were available, the enter method was used Significance level of 5% is indicated in bold type

Cox		T-Failure (365 events)		Primary locoregional failure (419 events)		Death from cancer (245 events)		Death from all causes (657 events)	
Variable	Number	p-value	RR (95% CI)	p-value	RR (95% CI)	p-value	RR (95% CI)	p-value	RR (95% CI)
Gender									
Female	145		**1.0**		**1.0**		**1.0**		**1.0**
Male	904	**0.004**	**1.6 (1.2–2.3)**	**< 0.000**	**1.7 (1.3–2.4)**	**0.001**	**2.1 (1.4–3.2)**	**< 0.000**	**1.6 (1.2–2.0)**
Regions		0.14		**0.006**		**0.008**		0.16	
Supraglottis	340		1.0		**1.0**		**1.0**		1.0
Glottis	690	**0.05**	**0.8 (0.6–1.0)**	**0.001**	**0.7 (0.5–0.9)**	**0.004**	**0.6 (0.5–0.9)**	0.13	0.9
Subglottic	19	0.96	1.0	0.66	0.9	0.14	0.5	0.16	0.7
T-stage		**< 0.000**		**< 0.000**		**< 0.000**		**< 0.000**	
T1a	382		**1.0**		**1.0**		**1.0**		**1.0**
T1b	135	**0.03**	**1.5 (1.0–2.3)**	**0.02**	**1.5 (1.0–2.2)**	**0.002**	**2.1 (1.3–3.5)**	**0.002**	**1.5 (1.2–2.0)**
T2	264	**< 0.000**	**2.1 (1.5–2.8)**	**< 0.000**	**1.9 (1.5–2.6)**	**0.007**	**1.8 (1.2–2.8)**	**0.004**	**1.4 (1.1–1.7)**
T3	184	**< 0.000**	**3.4 (2.4–4.7)**	**< 0.000**	**3.1 (2.3–4.2)**	**< 0.000**	**3.6 (2.4–5.5)**	**< 0.000**	**1.8 (1.4–2.3)**
T4	84	**< 0.000**	**3.6 (2.4–5.6)**	**< 0.000**	**2.8 (1.9–4.2)**	**< 0.000**	**3.8 (2.3–6.3)**	**< 0.000**	**2.3 (1.7–3.2)**
Nodal involvement									
N0	936		1.0		**1.0**		**1.0**		**1.0**
N+	113	0.91	1.0	**0.01**	**1.5 (1.1–2.0)**	**< 0.000**	**2.0 (1.4–2.7)**	**0.001**	**1.5 (1.2–2.0)**
Differentiation		**0.006**		**< 0.000**	**0.005**			0.07	
Well	409		**1.0**		**1.0**		**1.0**		1.0
Moderate	360	0.08	1.3	**0.02**	**1.3 (1.0–1.7)**	0.11	**1.4**	**0.04**	**1.2 (1.0–1.5)**
Poor	280	**0.002**	**1.6 (1.2–2.1)**	**< 0.000**	**1.7 (1.3–2.2)**	**0.001**	**1.8 (1.3–2.7)**	0.06	1.2
Hemoglobin									
High*	778		1.0		1.0		**1.0**		**1.0**
Low*	271	0.22	1.2	0.11	1.2	**0.002**	**1.5 (1.2–2.0)**	**< 0.000**	**1.4 (1.2–1.7)**

Abbreviation:. RR = relative risk.
*Cut-point: 7.90 mmol/L for females and 8.56 mmol/L for males.

on treatment outcomes, but preservation of the larynx is achieved in more patients. Many studies have tried to identify favorable or unfavorable prognostic determinants. We have evaluated relevant publications from the mid-1990s and onward. Only parameters reported as significant in multivariate analyses are mentioned and only if the same parameter was significant in our univariate analysis. Some publications only consider supraglottic tumors, some only glottic and some both anatomical regions. The significant parameters have been classified in relation to the patient, tumor or treatment.

The patient-related prognostic features were gender, age and hemoglobin. In a material of T1 laryngeal carcinomas, Carl et al. (13) found that females had better local control than men. This was also found in our series. In agreement with our findings Kowalski et al. (14) demonstrated a better survival rate for younger patients. In earlier publications the hemoglobin concentration has been demonstrated as a prognostic factor (15–17). In this presentation it was seen that, in a univariate analysis, a quarter of patients with low pretreatment hemoglobin had a poorer prognosis compared with the rest of the patients. In the multivariate analysis the hemoglobin value was a prognostic factor for 'death from cancer' and 'death from all causes'. One should be aware of the fact that the low hemoglobin in some patients could be an accidental finding, but in others could be a surrogate for poor performance status as a result of co-morbidity. Tarnawski et al. (15) confirmed a better local control and Nguyen-Tan et al. (17) a better survival with higher hemoglobin.

Many of the prognostic features were related to the tumor. T-stage was found to be highly prognostic for both locoregional control and survival. MacKenzie et al. (18) and Marshak et al. (19) showed a better local control with small tumors and Raitiola et al. (20) a better rate of survival in 293 Finnish laryngeal patients. MacKenzie et al. (18) documented N-stage as a prognostic factor for local control and Kowalski et al. (14) for survival. Jacobsen et al. (21) revealed the volume of lymph node metastases to be an independent, prognostic factor. Tumor size was described by Carl et al. (13) as significant for local control and by Bentzen et al. (22) for survival. Raitiola & Pukander (23) described tumor stage as significantly affecting disease-specific survival. Histological differentiation was prognostic for local control (13, 24, 25) and survival (24, 26), as patients with well-differentiated tumors were doing best. Several authors found the microscopic appearance of the

tumor as significant for both local control (27, 28) and survival (17, 29).

Duration of treatment was the treatment-linked prognostic feature, as Raitiola et al. (30) demonstrated a better survival time in patients undergoing short therapy in early glottic carcinomas.

Treatment recommendations have often evolved on basis of the results in different publications, and many have been implemented in local or national strategies. A problem with multivariate analyses seems to be that so many parameters are described as significant. Another limitation is the retrospective nature of the analyses, but the significant parameters in different studies may give a starting platform for new prospective studies.

The results varied during the different treatment periods. Local and locoregional control improved over time; disease-specific survival was unaltered, while overall survival was significantly decreased. Why was there no improvement in survival during the study period? There was no change in stage distribution over time, and other explanations such as an increase in treatment-related morbidity could not be demonstrated (1, 2). In the absence of a better explanation, more co-morbidity and changes of lifestyle in the larynx cancer population could be suggested.

As in other studies, the proportion of women with malignant tumors is rising. In the study period 14% of the patients were women, but this covers a rise over the treatment periods from 11%, over 14% and 15% to 17% in the last period. In the period from 1989 to 1998 the proportion of women in Denmark with laryngeal cancer was 18% (4). In the future one might expect that this frequency will continue to rise, as more and more women are smokers, a trend also described by Sanderson et al. in both a Dutch and a UK material (31, 32).

In conclusion, laryngeal carcinoma in an acceptable proportion is curable by primary radiotherapy, with a high degree of organ sparing. Multiple parameters were found significant in the univariate analyses. In the multivariate analyses independent prognostic factors were gender, region of origin of the tumors, T-stage, primary nodal involvement, histological differentiation of the tumor and pretreatment hemoglobin value.

ACKNOWLEDGEMENTS

We thank Else Marie Vinkle for excellent secretarial assistance. Lars Vendelbo Johansen's research was supported by the Danish Cancer Society and by Aarhus University.

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