Squamous Cell Carcinoma of the Oropharynx

An Analysis of Treatment Results in 289 Consecutive Patients

Lars Vendelbo Johansen, Cai Grau and Jens Overgaard

From the Department of Experimental Clinical Oncology Danish Cancer Society (L.V. Johansen, C. Grau, J. Overgaard), Department of Oncology (C. Grau) and the ENT Department (L.V. Johansen), Aarhus University Hospital, Aarhus, Denmark

Correspondence to: Lars Vendelbo Johansen, MD, ENT Department, Aarhus University Hospital, DK-8000 Aarhus C, Denmark. E-mail: larsvendelbo@dadlnet.dk

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In this retrospective study the results of primary and salvage treatment of oropharyngeal carcinoma were evaluated. A total of 289 consecutive patients (103 females and 186 males) were included in the study. Most tumours originated in the tonsil area (58%) and comprised stages I 8%, II 19%, III 46% and IV 28%. The primary treatment was delivered with curative intent in 276 cases (96%). Of these, 266 received primary radiotherapy. The median radiation dose was 62 Gy, given as laterally opposed fields to the primary tumour and bilateral neck. Eight patients were treated with primary surgery and two with chemotherapy as part of a curatively intended treatment programme including radiotherapy. Six patients received palliative treatment, and seven were not treated at all. Out of 276 tumours treated with curative intent, 173 reappeared; 72% recurred in T position, 38% in N position, and 12% at distant metastatic sites, some in combination. Salvage surgery was possible in 52 patients, and 24 treatments were successful. Salvage radiotherapy or cryotherapy was used in 22 patients and 4 were controlled. For the entire group, the 5-year locoregional tumour control, disease-specific survival and overall survival rates were 38%, 44% and 31%, respectively. For patients treated with curative intent, clinical T- and N-stage, stage, tumour size, gender, age, and pretreatment haemoglobin were significant prognostic parameters in a univariate analysis. The Cox multivariate analysis showed that T-stage, N-stage and gender were independent prognostic factors. It is concluded that T-stage, N-stage and gender are significant independent prognostic factors. The primary control of the carcinoma in the T-position is crucial for overall success, but salvage surgery is found to have a favourable success rate in patients suitable for relapse treatment.

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Cancer of the pharynx is rare, in 1994 accounting for only 0.7% of all malignant cases in Denmark, but the number of cases is rising. This is reflected in an increase in the total annual number of cases from 71 to 193 in the years 1975 to 1996 (1, 2) (minimum figures such as base of tongue tumours were reported along with tongue; rise 38–111 in the same period) and in the age-standardized incidence rates. Oropharyngeal cancers constitute 50% of these cases, of which more than 95% are squamous cell carcinomas. Epidemiological studies and clinical observations show that tobacco and alcohol use is strongly associated with the aetiology of oropharyngeal carcinomas, and the increase in incidence is trailing the curve for tobacco and alcohol abuse (3–6). Thus, in a French case-control study (3), only 1.6% of 634 men with oropharyngeal carcinoma were non-smokers and 2.7% were non-drinkers. The referred study also demonstrated a steep rise in the relative risk associated with tobacco and alcohol consumption. Tobacco and alcohol consumption is often closely related. The carcinogenic potential of tobacco and alcohol follows a multiplicative rather than an additive course (7), which, in combination with the shift in age distribution with a longer life expectancy, may explain the increasing frequency. Another French study demonstrated an increased incidence of oropharyngeal squamous cell carcinoma after liver transplantation for alcohol-related cirrhosis (8). In addition, industrial factors such as welding fumes should also be taken into account (9).

In Denmark cancer treatment is standardized, centralized and government funded. The treatment policy during the reported period has been that all patients should be considered for primary radiotherapy. The advantages of radiotherapy lie in organ preservation, as surgery in this area nearly always leads to functional and/or cosmetic defects. Another advantage with radiotherapy is sterilization of subclinical, microscopic nodal spread. The negative aspect is the induced morbidity, which increases with the volume treated.

Our institution receives all patients from a well-defined geographical area (1 million inhabitants). All patients are included in the present analysis, even those with advanced disease.

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Table 1

Primary symptoms in the 289 patients with oropharyngeal squamous cell carcinoma. A maximum of three symptoms was recorded for each patient

Sore throat	159 (55%)
Dysphagia	100 (35%)
Enlarged lymph node(s)	76 (26%)
Ear pain	58 (20%)
Loss of weight	18 (6%)
Spacious process	13 (4%)
No symptoms	6 (2%)

Table 2

Tumour origin oropharynx (UICC 1982)

Anterior wall	
Tongue posterior to the vallate papillae	48 (17%)
Vallecula	15 (5%)
Anterior (lingual) surface of epiglottis	5 (2%)
Lateral wall	
Tonsil	149 (52%)
Tonsillar fossa and faucial pillars	19 (7%)
Glosso-tonsillar sulci	1 (0%)
Posterior wall	19 (7%)
Superior wall	
Inferior surface of soft palate	30 (10%)
Uvula	3 (1%)
Total	289 (100%)

In 1976 (10), 1987 (11) and in 1990 (12) papers from our centre studying malignant tumours of the oropharynx have been published and many of the patients have been re-evaluated and reappear in this publication.

The aim of this study was to evaluate prognostic factors for tumour control, treatment of recurrences and survival in an unselected series of patients with squamous cell carcinoma of the oropharynx including palliative or non-treated patients.

MATERIAL AND METHODS

The patient material consisted of 289 consecutive patients referred to the head and neck oncology team, Aarhus University Hospital, from January 1963 to December 1991. Of these patients, 103 (36%) were females and 186 (64%) were males. The median age was 65 years (range 24–93 years). The most frequent symptoms were sore throat, dysphagia, enlarged lymph nodes and otalgia (Table 1). The diagnostic work-up included evaluation and biopsy under general anaesthesia by an experienced head and neck surgeon, chest x-ray and routine blood tests. The neck was examined by palpation only, but in later years also by ultrasound and CT/MR-scanning if there was some uncertainty. All the patients had biopsy-proven squamous cell carcinoma. The histological grading was recorded in 198 patients; 26% were well differentiated, 24% moderately and 50% poorly differentiated. Many of the tumours originated in the tonsils (52%), fewer from the base of tongue or soft palate (Table 2). A large proportion, 175 (61%), of the patients had metastatic lymph nodes at presentation, the most frequently involved region being the subdigastric area (Fig. 1). All patients were classified according to the UICC 1982 classification (13). The distribution, based on T- and N-classification, is shown in Table 3. The majority of cases were in Stage III (46%) or IV (28%) at the time of diagnosis. Three patients had distant metastases at presentation.

The primary treatment was delivered with curative intent in 276 of 289 cases (96%). Of the patients treated

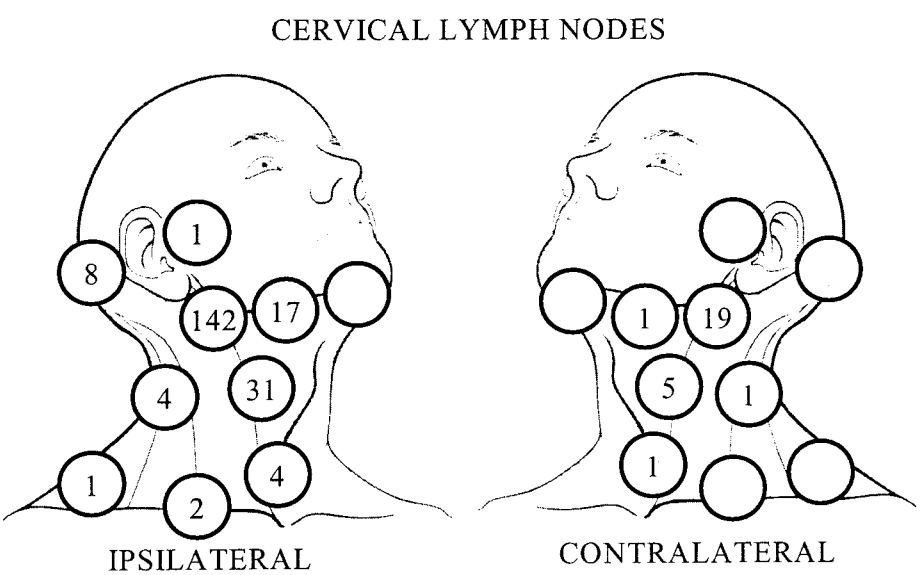

Fig. 1. Localization of metastatic lymph nodes in 175 node-positive patients. Part of 289 patients with squamous cell carcinoma of the oropharynx.

Table 3

The stage distribution of the 289 patients with oropharyngeal squamous cell carcinoma (UICC 1982)

	N0	N1	N2	N3	Total
T1	22	21	2	7	52 (18%)
T2	54	48	7	17	126 (44%)
T3	33	30	3	31§	97 (34%)
T4	5	4+	1	3	13 (4%)
TX				1 #	1
Total	114 (39%)	103 (36%)	13 (4%)	59 (20%)	289

Stage I = 22 (8%); Stage II = 54 (19%); Stage III = 132 (46%); Stage IV = 81 (28%).
Distant metastases:
§ One patient with T3N3M1.
+ One patient with T4N1M1.
# One patient with TXN3M1.

radically, the majority (266 out of 276) received primary radiotherapy, in 11 cases combined with some form of surgical procedure (e.g. neck dissection, tonsillectomy, excision of tumour in base of tongue). Eight patients were treated by surgery alone in the form of a tonsillectomy, a pharyngectomy or excision of a tongue tumour, some in combination with neck dissection. Two patients were scheduled for combined chemotherapy and radiotherapy with curative intent, but died before the start of radiotherapy. Six patients received palliative treatment (5 radiotherapy, 1 surgery), and 7 were not treated at all. The standard radical radiotherapy technique was parallel opposing lateral fields using cobolt-60 in 205 pts (77%), or 4-6-8 MV photons in 61 pts (23%). One patient was treated with a single field and two patients with wedged pairs. Missing tissue compensation was done in all cases. CT dose planning was done in some of the cases in the last part of the study period. The treatment schedules are listed in Table 4. Thirty-nine patients, treated in the first part of the study period, were treated with one field per day, whereas the remaining patients were treated on all fields each day. Prophylactic neck irradiation of clinically non-involved regions to a dose of 46–50 Gy was applied using a shrinking field technique. Shielding of the spinal cord was done at the same time after 46–50 Gy, and any involved posterior neck was treated to the high dose with electrons. The median initial field size was equivalent to 96 cm^2. To compensate for variations in the biological effect of different fraction sizes, the total radiation dose actually delivered was recalculated as the biological equivalent given in 2 Gy fractions using an α/β ratio of 10 Gy for tumour response. This dose ranged from 6 to 76 Gy, with a median of 62 Gy. There was a tendency towards using a linear accelerator (instead of cobalt) and higher total doses (66–68 Gy) in the last part of the study period. Sixty-six patients were treated with split-course radiotherapy, i.e. a 3-week gap after the first part of the treatment; 9 patients scheduled for this strategy did not complete the treatment. Forty-five patients received a chemical radiosensitizer, either misonidazole or nimorazole, as a part of the randomized trials DAHANCA 2 (14) and DAHANCA 5 (15). Nine patients were included in the DAHANCA I phase II study of the effect of administration of bleomycin, methotrexate and vincristine before irradiation (16).

Patients were followed-up at regular intervals at the University Hospital for a period of 5 years after treatment and were always assessed jointly by specialists in the ENT and oncology departments. Their disease status and survival parameters were routinely documented in the patient chart. For the present analysis, all charts were reviewed for details about tumour status. The survival status of all patients was updated per May 1, 1998 and cross-checked with the Central Population Registry (to check vital status; eventual cause of death was also explored) and the National Cancer Register. The data were recorded in a Medlog® personal computer database and analysed by the univariate Kaplan–Meier method using the SPSS/PC® computer software. Differences between parameter estimates were compared using a log-rank test with a significance level decreased from 5% to 1% to avoid problems with mass significance. The independent significance of parameters was tested in a multivariate Cox proportional hazards model (in these analyses, we used a significance level of 5%).

Table 4

Treatment schedules: 266 patients received primary radiotherapy with curative intent. All patients were treated with 5 fractions per week

Period	No. of patients in period	Treatment policy
01.01.63–30.06.70	38	57 Gy/30 fx
01.07.70–31.12.77	64	60 Gy/30 fx
01.01.78–31.01.85	75	40 Gy/20 fx – 3 wk split- 28–32 Gy/14–16 fx
01.02.85–31.12.85	16	60 Gy/30 fx
01.01.86–31.12.91	73	66–68 Gy/33–34 fx

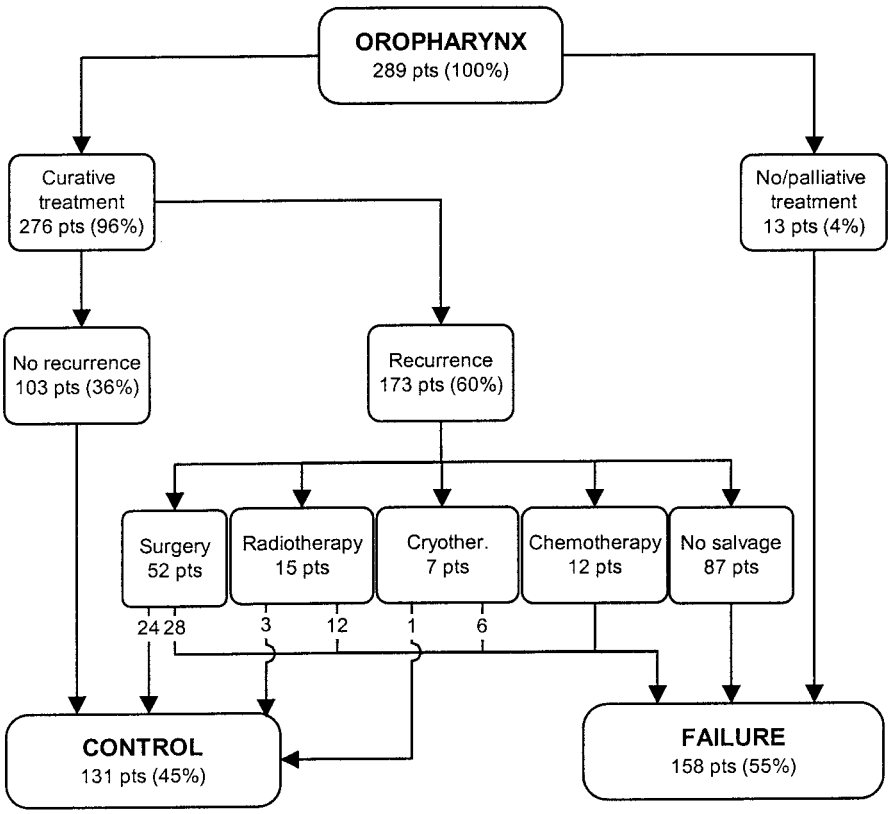

Fig. 2. The clinical course from diagnosis to tumour control or treatment failure in 289 patients with oropharyngeal squamous cell carcinoma.

RESULTS

At the time of analysis 62 of the 289 patients were alive. Fifty-one patients were alive without recurrence, 9 were disease-free after salvage treatment and 2 had active disease.

The clinical course from diagnosis to either tumour control or failure is shown in Fig. 2. Of the 276 patients treated with a curative intent, a total of 173 (60%) had residual tumours or developed recurrent disease. Of these, 58 could be treated with a new curative intent, and 28 were successfully salvaged this way. Consequently, 131 patients (45%) were controlled, and of these, 17 patients in turn died as a result of the development of new primaries; 4 in the head and neck region, 5 in the respiratory tract and 8 had other types of malignant disease. Two patients died of complications without sign of recurrence, one of chemotherapy complications and the other as a result of necrosis in the tonsillar region.

Salvage treatment in patients with residual tumour or recurrence was surgery in 52 cases. The procedures used were partial pharyngectomy inclusive resection of base of tongue, laryng-pharyngectomy and lymph node dissection. In three patients the surgical procedure was combined with radiotherapy. Twenty-four patients were salvaged by surgery, 13 by pharyngectomy and 11 by lymph node dissection, in two patients surgery was combined with radiotherapy. As can be seen in Fig. 2, 15 patients were treated by irradiation after recurrence, 7 treatments were with curative intent and 3 were controlled this way (two of these patients had surgery as primary treatment). Seven patients had cryotherapy as salvage treatment in the first part of the study period and one of the patients was controlled after several treatments.

The eight patients treated surgically and the two treated with chemotherapy are included in the present analysis of patients treated with curative intent. Five of the patients treated surgically were controlled, three after recurrence treatment; three died from recurrent disease. The two patients treated with chemotherapy both died, one following bone marrow depression after induction chemotherapy before the scheduled radiation treatment had started. The other patient got worse under chemotherapy and never started radiotherapy.

The failure patterns for the 276 patients treated with curative intent are presented in Fig. 3. Recurrences in the primary site (T recurrence) or in the neck (N recurrence) were predominant, and often in combination. Isolated N recurrences were seen in 35 patients, 15 being classified as N0 on admission (T1: 4, T2: 9, T3: 2, T4: 0) and 20 as N + (T1: 3, T2: 10, T3: 7, T4: 0). Isolated distant metasta-

sis (M recurrence) was rare and only seen in 10 patients (3.6%). In 103 patients (37%) no recurrence was seen.

The overall 5- and 10-year actuarial estimates for tumour control and survival for the entire group of 289 patients are shown in Table 5. The disease-specific survival rate was slightly higher than the locoregional control rate, since some patients with recurrences had successful salvage treatment.

In the study of prognostic parameters for treatment outcome, only the 276 patients treated with a curative intent were included. The results of univariate Kaplan–Meier analyses of T control, N control, locoregional control, disease-specific survival and overall survival for various, but selected parameters are listed in Table 6 with 5-year values (and 10-year values for overall survival). Younger patients and females had better prognoses. Tumour stage was very important for the prognosis, both in terms of locoregional control (Fig. 4) and disease-specific survival (Fig. 5). Patients with T1 tumours had a 5-year locoregional control rate of 59% compared with 0% for patients with T4 tumours. Similarly, T1 patients had a 5-year disease-specific survival rate of 65% compared with 9% in T4 patients. Other significant factors were N-stage, tumour volume (largest diameter in T site) and pre-treatment haemoglobin level. Clinical stage was also important, but there was no difference between stages I to III (Figs. 6 and 7). Neither radiotherapy dose nor overall treatment time or treatment period had a significant influence on the treatment outcome.

The data were analysed in a Cox proportional hazards model (Table 7). The independent significant parameters were T-stage, N-stage and gender. Haemoglobin level was significant only for T control.

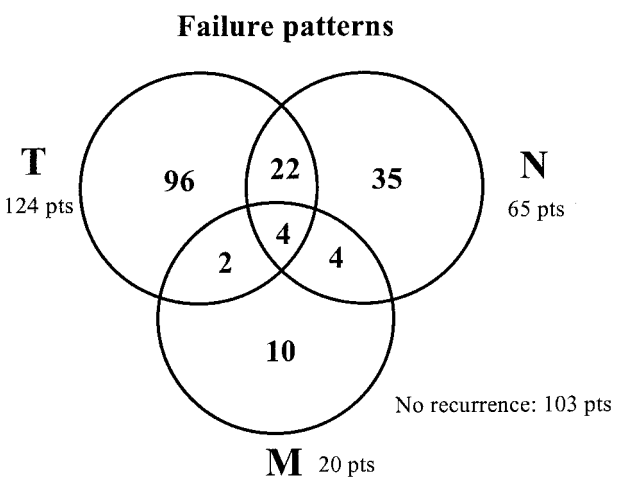

Fig. 3. Failure patterns in the 276 patients treated with curative intent for oropharyngeal carcinoma. In 103 patients, no recurrences were seen.

Table 5

Kaplan–Meier estimates at 5 and 10 years for various tumour and survival endpoints in 289 patients with oropharyngeal squamous cell carcinoma. Thirteen of these patients received palliative or no treatment; the remaining 276 patients were treated with a curative intent

End point	5-year (%)	10-year (%)
Tumour control	51	43
Neck control	71	68
Locoregional control	38	31
Distant metastasis free	89	88
Disease-specific survival	44	39
Overall survival	31	23

DISCUSSION

Primary radical radiotherapy has been the treatment of first choice for all oropharyngeal carcinomas in Denmark during the last decades, and surgery has been reserved for salvage. This has been the accepted strategy by all head and neck surgeons and radiation oncologists in Denmark and also at our institution, so the selection bias in the present series is minimal.

The data show that survival depends essentially on the primary control of the tumour in the T position (17, 18). Salvage procedures have some effect, as 48% (28/58) of the patients who had attempted curative salvage treatment were controlled, but this is still only a small proportion, 34% (58/173), of the patients with recurrence who can have a curative salvage attempt. The goal should be to eradicate the disease using the initial treatment modality, combined with a minimum of treatment morbidity. One way to reduce the morbidity is to limit the irradiated volume. This can be done by irradiating only the ipsilateral side of the neck in lateral tumours, such as tonsillar carcinomas (19).

We found a high incidence of nodal metastases (61%), which has also been observed in other studies (20, 21). This contrasts with the more moderate incidence of one-third in carcinomas of the oral cavity and 3% of the glottic larynx. Nodal control was acceptable and, surprisingly, it was found that stages I, II and III had the same locoregional control and survival (Figs. 6 and 7). In fact, it can be seen from Table 6 that T1 was doing better than T2 and T3, indicating that the favourable prognosis of lower T-stage is clearly influenced by nodal involvement.

Tumour origin was also analysed in the univariate analysis, grouped by the sites, and there was no prognostic difference between tumours, originating in either the base of the tongue area or the tonsil area. Others also reported this finding, even in advanced cases (22). In our material distant metastases were relatively rare phenomena (7%) and were frequently discovered along with a locoregional recurrence, while other workers report a higher incidence (21). The dominating problem remains the isolated recurrences in the T position, in our material amounting to 55% of the recurrences (33% of all the patients).

Table 6

Univariate actuarial analysis of prognostic factors for the 276 patients with oropharyngeal squamous cell carcinoma treated with curative intent. Listed percentages are 5-year Kaplan–Meier estimates for T control, N control, locoregional control and disease-specific survival ± SE. Overall survival listed by 5- and 10-year values. Significant differences (1% level) marked in bold type

Parameter	No. Pts.	T control	N control	Locoregional control	Disease-specific survival	Overall surv. 5-year	Overall surv. 10-year
All patients	276	53 ± 3	71 ± 3	40 ± 3	46 ± 3	33 ± 3	24 ± 3
Female	101	**69 ± 5**	65 ± 5	**52 ± 5**	**58 ± 5**	**45 ± 5**	**32 ± 5**
Male	175	**43 ± 4**	60 ± 4	**32 ± 4**	**39 ± 4**	**26 ± 3**	**19 ± 3**
Age 18–65	143	55 ± 4	64 ± 4	43 ± 4	51 ± 4	**39 ± 4**	**31 ± 4**
65+	133	50 ± 5	59 ± 5	36 ± 5	42 ± 5	**26 ± 4**	**17 ± 3**
Tongue/vallecula	67	53 ± 6	63 ± 6	39 ± 6	39 ± 7	31 ± 6	22 ± 5
Tonsil/tons. fossa	161	51 ± 4	60 ± 4	40 ± 4	47 ± 4	36 ± 4	27 ± 4
Posterior wall	16	81 ± 10	46 ± 13	42 ± 13	44 ± 14	13 ± 8	6 ± 6
Soft palate/uvula	32	46 ± 10	78 ± 9	38 ± 9	55 ± 10	34 ± 8	23 ± 8
T1	51	**73 ± 7**	**80 ± 6**	**59 ± 7**	**62 ± 8**	**46 ± 7**	**29 ± 7**
T2	124	**59 ± 5**	**71 ± 5**	**42 ± 5**	**51 ± 5**	**38 ± 4**	**34 ± 4**
T3	90	**41 ± 6**	**70 ± 6**	**32 ± 5**	**35 ± 5**	**22 ± 4**	**11 ± 3**
T4	11	**0**	**0**	**0**	**9 ± 9**	**0**	**0**
N0	112	**53 ± 5**	**79 ± 4**	**41 ± 5**	**49 ± 5**	**37 ± 5**	**27 ± 4**
N1	98	**65 ± 5**	**72 ± 5**	**46 ± 5**	**56 ± 5**	**38 ± 5**	**30 ± 5**
N2	13	**59 ± 14**	**86 ± 13**	**59 ± 14**	**56 ± 15**	**38 ± 13**	**19 ± 12**
N3	53	**32 ± 7**	**40 ± 10**	**20 ± 6**	**20 ± 6**	**13 ± 5**	**8 ± 4**
Stage I	22	**61 ± 12**	**73 ± 11**	**45 ± 11**	**50 ± 12**	**32 ± 10**	**23 ± 9**
Stage II	53	**61 ± 7**	**77 ± 6**	**46 ± 7**	**53 ± 7**	**45 ± 7**	**41 ± 7**
Stage III	128	**59 ± 5**	**68 ± 4**	**45 ± 5**	**55 ± 5**	**37 ± 4**	**25 ± 4**
Stage IV	73	**33 ± 6**	**36 ± 6**	**25 ± 5**	**26 ± 5**	**16 ± 4**	**9 ± 3**
Low haemoglobin*	137	**44 ± 5**	60 ± 5	36 ± 4	42 ± 5	**29 ± 4**	**19 ± 3**
High haemoglobin	111	**65 ± 5**	65 ± 5	46 ± 5	54 ± 5	**39 ± 5**	**31 ± 4**
T-size 1–19 mm	35	**73 ± 8**	**81 ± 7**	**60 ± 9**	**68 ± 9**	**50 ± 9**	**38 ± 8**
20–39 mm	112	**63 ± 5**	**65 ± 5**	**45 ± 5**	**53 ± 5**	**38 ± 5**	**32 ± 4**
40–59 mm	106	**39 ± 5**	**56 ± 5**	**30 ± 5**	**37 ± 5**	**26 ± 4**	**15 ± 4**
60+ mm	23	**31 ± 10**	**49 ± 11**	**27 ± 10**	**21 ± 11**	**9 ± 6**	**4 ± 4**
Well differentiated	49	54 ± 8	63 ± 7	41 ± 8	46 ± 8	31 ± 7	22 ± 6
Moderately different	47	45 ± 8	65 ± 8	36 ± 7	47 ± 8	28 ± 7	21 ± 6
Poorly differentiated	92	53 ± 5	58 ± 6	40 ± 5	39 ± 5	30 ± 5	22 ± 4
RT dose 2–59 Gy #	110	54 ± 5	59 ± 5	43 ± 5	48 ± 5	32 ± 4	25 ± 4
60–65 Gy	103	52 ± 6	65 ± 5	37 ± 5	43 ± 5	33 ± 5	22 ± 4
66+ Gy	53	51 ± 7	63 ± 7	41 ± 7	49 ± 7	33 ± 7	23 ± 6
RT time ≤ 50 days	155	54 ± 4	61 ± 4	43 ± 4	46 ± 4	31 ± 4	21 ± 3
51+ days	105	53 ± 5	62 ± 5	36 ± 5	43 ± 5	31 ± 5	25 ± 4
Treatment period							
63–70 (~57 Gy)	39	45 ± 9	59 ± 8	36 ± 8	50 ± 9	31 ± 7	23 ± 7
70–78+85 (~60 Gy)	83	54 ± 6	66 ± 6	43 ± 6	51 ± 6	33 ± 5	22 ± 5
78–85 (split cor.)	80	55 ± 6	61 ± 6	38 ± 6	42 ± 5	33 ± 5	29 ± 5
86-91 (~66 Gy)	74	52 ± 6	60 ± 6	39 ± 6	44 ± 6	34 ± 6	20 ± 5

* Cut point: 8.0 mmol/L for females and 9.0 mmol/L for males.
# Total delivered radiation dose in 2 Gy/fraction equivalence ($\alpha/\beta = 10$ Gy).

Isolated failure in the N position was seen in 35 patients. At the primary work-up 15 of these patients were classified, as N0 and the treatment field did not specifically take care of these clinical negative nodes. It could be speculated whether these 5% could have benefited from neck dissection if this procedure had been included in the primary treatment protocol. The next question would be whether all patients with N0 (112) or all patients treated with curative attempt (276) ought to have neck dissections.

In a material of 490 patients with oropharyngeal carcinomas it was reported that radiotherapy treatment results in tumour control and survival rates comparable with those achieved with combined irradiation and surgery, with less morbidity (21). A study including 105 patients reported equal success using radiotherapy or surgery (23). Another study comprising 51 patients with advanced base of tongue and tonsillar fossa tumours reported good results with combined surgery and radiotherapy (22). In one material analysing 102 tonsillar carcinomas, it was also found that combined treatment with surgery and radiotherapy yielded the best results (24). One presentation on 90 tonsillar carcinomas found that small tumours, stage I/II, did equally well with radiotherapy or surgery alone, but that large tumours were best treated with radiotherapy (25). One group, studying 384 patients with tonsillar fossa carcinomas, stated that the treatment modality had no significant impact on outcome when comparing pre- and postoperative irradiation with radiotherapy alone (26). Ipsilateral irradiation of patients with carcinomas of the tonsil gave survival results as favourable as those reported with bilateral treatment and with fewer side effects, such as late morbidity, and with a lower risk of failure in the contralateral neck (19).

Interstitial treatment alone or combined with external radiotherapy gave better results when compared with external radiation alone (27). This was also observed in a

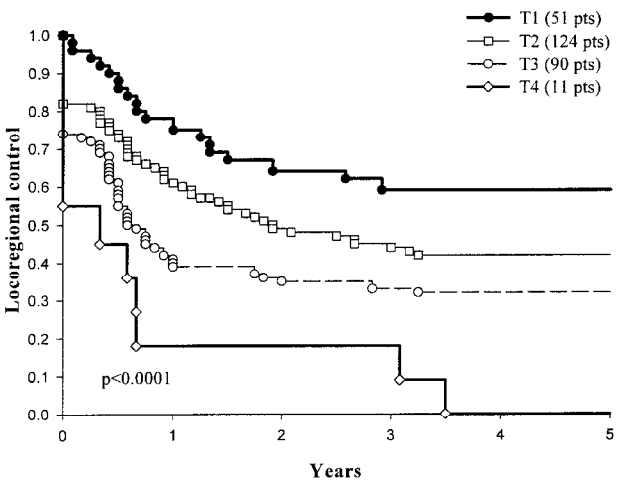

Fig. 4. Locoregional tumour control. T classification for 276 patients treated with radical intent.

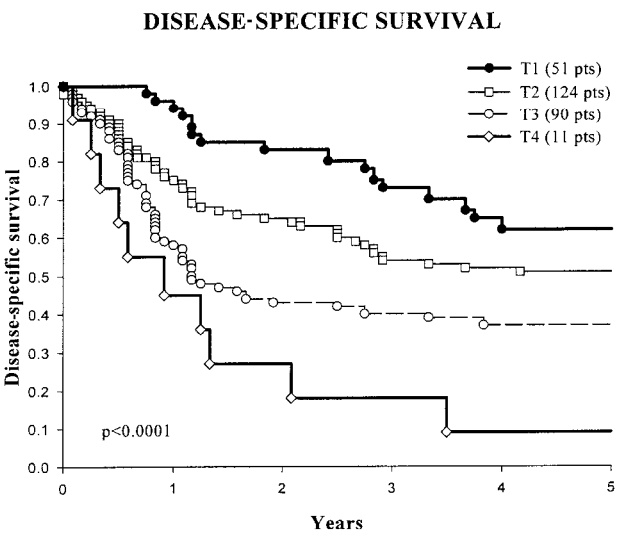

Fig. 5. Disease-specific survival. T classification for 276 patients treated with radical intent.

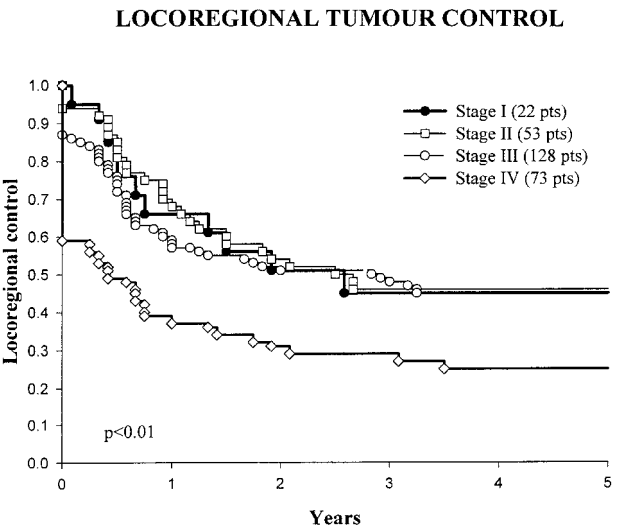

Fig. 6. Locoregional tumour control. Clinical stages for 276 patients treated with radical intent.

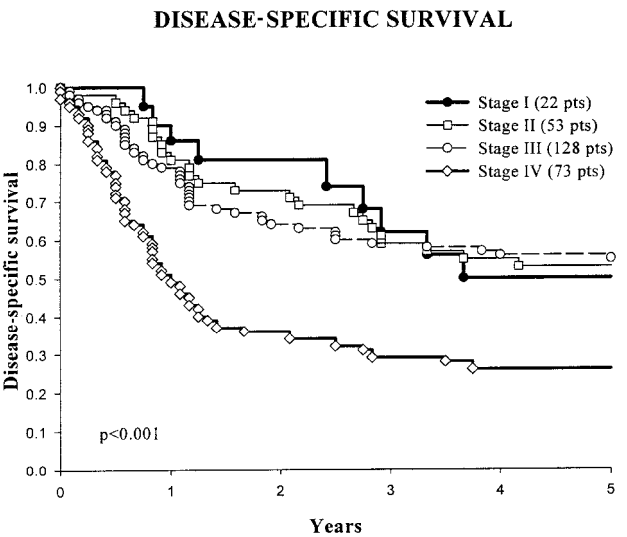

Fig. 7. Disease-specific survival. Clinical stages for 276 patients treated with radical intent.

Table 7

Cox proportional hazards analysis of prognostic factors for treatment outcome in 276 patients with oropharyngeal squamous cell carcinoma treated with curative intent. The analysis includes 248 patients for whom all listed parameters are available

Cox variable	Number	T failure (109 events)		Neck failure (60 events)		Locoreg. failure (144)		Death f. cancer (127)	
		p-value	RR (95% CI)	p-value	RR (95% CI)	p-value	RR (95% CI)	p-value	RR (95% CI)
T-stage		**0.000**		0.31		**0.002**		**0.001**	
T1	40		1.0		1.0		1.0		1.0
T2	113	0.60	1.2	0.20	1.7	0.26	1.4	0.34	1.3
T3	84	**0.04**	**2.1 (1.1-4.0)**	0.17	1.8	**0.01**	**2.0 (1.2-3.6)**	**0.01**	**2.1 (1.2-3.9)**
T4	11	**0.000**	**4.7 (2.0-11.0)**	0.07	3.2	**0.001**	**3.8 (1.7-8.3)**	**0.001**	**4.1 (1.8-9.4)**
N-stage		**0.02**		**0.000**		**0.03**		**0.000**	
N0	95		1.0		1.0		1.0		1.0
N1	93	0.86	1.0	0.22	1.5	0.63	1.1	0.41	1.2
N2	12	0.56	1.3	0.47	0.5	0.87	0.9	0.45	1.4
N3	48	**0.005**	**2.0 (1.2–3.2)**	**0.000**	**3.8 (2.0-7.4)**	**0.004**	**1.9 (1.2-3.0)**	**0.000**	**2.7 (1.7-4.2)**
Gender									
Female	93		1.0		1.0		1.0		1.0
Male	155	**0.000**	**2.2 (1.4-3.3)**	0.58	1.2	**0.002**	**1.8 (1.2-2.5)**	**0.007**	**1.7 (1.2-2.5)**
Haemoglobin*									
High	111		1.0		1.0		1.0		1.0
Low	137	**0.03**	**1.6 (1.1-2.3)**	0.30	0.8	0.32	1.2	0.11	1.3

* Cut point: 8.0 mmol/L for females and 9.0 mmol/L for males.
RR = relative risk.

study using fractionated high-dose-rate and pulsed-dose-rate brachytherapy regimens, which simulate classical continuous low-dose-rate interstitial radiation therapy schedules (28).

One way to get better results with radiotherapy is to deliver the treatment in multiple, small fractions (hyperfractionation) (29, 30). A large EORTC study comprising 356 patients demonstrated the therapeutic advantage of such a strategy (31). This was also seen in a smaller study with 99 patients (32). Another approach is to shorten the overall treatment time in order to reduce the influence of repopulation of tumour cells during the treatment (33). These schemes can be combined as in the CHART study randomizing 918 patients with head and neck carcinomas (34). The addition of a chemical hypoxic cell radiosensitizer such as nimorazole also improved the prognosis for patients with pharyngeal tumours (15).

There have been many studies on chemotherapy in the treatment of head and neck squamous cell carcinoma. A meta-analysis involving over 10 000 patients concludes that there was a small statistically significant benefit to survival (7–8%) when concomitantly multiagent chemotherapy was added to loco-regional treatment, but that the routine use of chemotherapy remains debatable taking into consideration such a small benefit (35). In an editorial, Forastiere & Trotti (36) recommend 'radiochemotherapy as a standard of care for locally advanced oropharyngeal cancer'. They base their recommendation on several clinical trials, e.g. one by Calais et al. (37) who added three cycles of chemotherapy during standard radiation therapy, demonstrating statistically significant improvement in locoregional control, disease-free survival and overall survival. Other randomized studies (38–41) on advanced head and neck cancer comparing radiotherapy with concurrent radiochemotherapy support these findings. Acute and in particular late effects have to be evaluated; to preserve the organ is not justifiable if late effects such as mucosal injury and fibrosis hinder the function. It is hoped that the results of ongoing and future studies will give further insight into these aspects.

In conclusion, T-stage, N-stage and gender are significant independent prognostic factors. The primary control of the carcinoma in the T position is crucial for overall success, but salvage surgery is found to have a favourable success rate in patients suitable for relapse treatment.

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