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Treatment of Squamous Cell Carcinoma of the Oral Cavity, Oropharynx and Hypopharynx

An Analysis of 174 Patients in South Western Finland

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The purpose of this study was to determine the efficacy and feasibility of full-dose preoperative radiation therapy (RT) in head and neck cancer presenting in the oral cavity, oro- and hypopharynx, within a single university hospital district. During a seven-year period, 1989 to 1995, 174 patients with squamous cell carcinoma (SCC) of the oral cavity (OC, 70% of all patients), oropharynx (OP, 15%) and hypopharynx (HP, 15%) were referred to Turku University Central Hospital. All patients were seen by a tumor board consisting of an ENT (ear–nose–throat) head and neck surgeon, a radiation oncologist and a dentist. Potentially curative treatment was given to 142 patients. Of these, 88 (62%) had preoperative RT, 6 (4%) postoperative RT, 34 (24%) definitive RT and 14 patients (10%) were treated with surgery only. The radiation dose was ≥ 50 Gy, averagely 64 Gy. The major endpoints of the study were local control, overall survival and major complications of the combined treatment. The 5-year relative survival rate (RSR) was 40% for all, and 43% for patients treated with curative intent. For these, the local control at 5 years was 60%; the disease-specific 5-year survival rate was 65% for the patients with lingual SCC, 45% for those with other oral tumor localizations, 64% for the oropharynx patients and 47% for those with tumor in their hypopharynx, while it was 55% for all patients. The preoperative radiotherapy was fairly well tolerated. Ten (7%) of the patients treated with curative intent suffered major complications, and four patients had evidence of osteoradionecrosis. With the exception of patients with early SCC the outcome remains rather poor in this group of cancer patients who often have marked co-morbidity. In our opinion, preoperative radiotherapy to a dose of 62–64 Gy can safely be given, and remains a feasible means to treat patients with oral, oropharyngeal or hypopharyngeal cancer.

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The annual number of new head and neck carcinoma patients in Finland is approximately 630, i.e. 3% of all cancer cases in Finland. During the last two decades the number of new cases of cancer of the mobile tongue has doubled, while that of pharyngeal cancer has increased more slowly, but in contrast the incidence of laryngeal cancer has decreased (1–4). Frequency has increased in particular among women in these groups (5). The overall survival of patients with carcinoma of the oral cavity has not changed much during recent decades. It is largely determined by the stage of the disease (6).

The standard treatment of cancer of the oral cavity (OC), oro- (OP) and hypopharynx (HP) is surgery, combined, in larger tumors, with postoperative radiotherapy (RT), although the literature seems to suggest that small tumors in the tonsillar area can also be controlled with definitive RT (7). The combined methods are becoming increasingly popular, as they are considered to produce better locoregional results. Postoperative RT is the preferred treatment modality globally. However, preoperative RT theoretically has certain advantages. Preoperative RT may reduce the rate of positive margins at surgery and is not compromised by the impaired tissue oxygenation caused by the surgical intervention. Furthermore, preoperative RT has been shown to reduce the quantity of cervical nodes harboring viable cancer (8), and has not predisposed the patients to possible complications in free tissue transfers (9). On the other hand, preoperative radiation may alter local or lymphatic metastatic invasion. Many surgeons also fear the possible complications associated with preoperative irradiation such as impaired wound healing (10, 11).

Generally, our treatment protocol for head and neck squamous cell carcinoma (HNSCC) in Turku University Central Hospital (TUCH) has since 1988 been preoperative

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RT and surgery. The purpose of our study was to determine the efficacy and feasibility of treatment procedures consisting of preoperative radiation therapy and surgery in patients with oral cavity, oropharyngeal and hypopharyngeal cancer seen in a single institution during a period of 7 years. We analyzed local control and survival, and major complications with the aim of elucidating whether our protocol fares as well as the more generally used surgery and postoperative RT.

MATERIAL AND METHODS

Data collection

Patient data were retrospectively collected from the hospital database, and the information was also manually checked from the patient charts. The cohort of this study consists of the 174 patients who were referred to Turku University Central Hospital (TUCH) with head and neck squamous cell carcinoma (HNSCC) in the oral cavity, oropharynx or hypopharynx between January 1989 and December 1995. TUCH is a tertiary referral center responsible for treating new HNSCC cases from the provinces of South Western Finland, Satakunta and Ahvenanmaa. In 1991, 696 000 citizens were living in the catchment area of TUCH.

Patients and tumors

The patient charts were reviewed. The primary investigations consisted of a careful physical examination, panendoscopy including broncho-oesophago-gastroscopy, computed tomography (CT) scans from the primary tumor area and neck, chest x-ray and ultrasonography with fine-needle aspiration biopsy when indicated. The planning of the treatment was determined by a tumor board consisting of a team of otorhinolaryngology—head and neck surgeons, radiation oncologists and dentists. Before irradiation, all the patients were referred for dental examinations and for any prophylactic treatment required.

The patient group consists of 174 patients with 176 tumors. The baseline characteristics of the patients (82 women and 92 men) are listed in Table 1. Two of the male patients had two separate malignancies in the head and neck area concurrently. One had a T1N0 cancer of the tongue on the right side and a T2N0 cancer on the left side of the floor of the mouth, and the other had a T1N0 buccal cancer and a T1N0 cancer of the retromolar triangle of the left upper gingiva. The tumors were staged according to the UICC TNM classification (see Table 2) (12). The Zubrod index was routinely obtained from patient records (13). The male/female ratio in the tongue carcinoma group was 24/36 (14/21% of the whole population) in the group with tumors localized elsewhere in the oral cavity 36/25 (21/14%), in the oropharynx group 15/12 (9/7%) and in the hypopharynx group 17/9 (10/5%).

Table 1

Patient (n = 174) and tumor characteristics

		No. of patients	%
Age (yrs)	Mean	67	
Sex	Male	92	53
	Female	82	47
Zubrod index	0	18	10
	1	107	61
	2	42	26
	3	7	4
Histological grade, n = 176[1,3]	1	80	45
	2	65	37
	3	20	11
	Not available	11	6
Type of tumor[2,3]	Ulcerative	42	24
	Exophytic	47	27
	Mixed, other	85	48
Side[3]	Left	91	52
	Right	70	40
	Other	15	9
Tumor localization[3]	OC—mobile tongue	60	34
	OC—other	61	35
	Oropharynx	27	16
	Hypopharynx	26	15

[1]Eleven specimens were not available for re-evaluation.
[2]information was missing for two patients.
[3]Two of the 174 patients had two synchronous tumors.

Table 2

Squamous cell carcinoma of the head and neck region according to UICC Classification (n = 176)[1]

Class	Tongue	Oral cavity	Oropharynx	Hypopharynx
	No. of patients			
T1	16	8	4	4
T2	26	22	12	9
T3	18	8	4	4
T4	2	23	7	9
N0	46	40	16	13
N1	12	15	7	9
N2	4	6	2	4
N3	0	0	2	0
M0	61	60	26	26
M1	1	1	1	0

The smoking and alcohol consumption habits were recorded in 95% and 74% of male, and 83% and 73% of female patients, respectively. The highest alcohol consumption rate was recorded in hypopharyngeal cancer patients (33%) and the lowest rate among tongue cancer patients (15%). Among women, 68% (46/68) and among men 16% (14/87) were non-smokers. Non-smokers were most com-

mon among tongue cancer patients (45%) and smoking was most regular among hypopoharynx cancer patients (69%).

There were 80 early, Stage I (T1N0) and Stage II (T2NO) cases, and 96 advanced cases, Stage III–IV, with two patients having two tumors. The incidence of cervical lymph node metastases was 26% for tongue cancer patients, 34% for other OC, 40% for OP, and 50% for HP cancer patients, respectively. In 11 cases (6%), the lymph node metastases were bilateral. Distant metastases were found in only three patients at the time of diagnosis.

The median hemoglobin level at the beginning of radiotherapy in the group of curatively treated patients was 134 g/dL (range, 88–167 g/dL). The time from the first symptoms to diagnosis ranged from 0 to 96 months. Twenty-two patients had had symptoms for at least 12 months.

Histopathological analysis

A complete histopathological review of all tissue slides was retrospectively carried out by an experienced pathologist (P.K.), who graded all tumors according to the International Histological Classification of Tumors (14). Only tumors with a histological diagnosis of squamous cell carcinoma were included in the final analysis. Among those were two patients who had a verrucous carcinoma. The histological specimens were not available for re-evaluation in 11 cases. Two patients had a primary biopsy only from a cervical lymph node metastasis. Characterizations of the tumors are presented in Table 1.

TREATMENT METHODS

Preoperative radiotherapy (RT) has been used as a standard management of HNSCC in our hospital since 1988. One exception is early (T1-2N0) lingual cancer, where radical surgery is the preferred treatment modality (15). The second exception is early tonsillary carcinoma, where RT is given after the surgery for the primary tumor. On the other hand, in T1–2 hypopharyngeal cancer, RT is the principal treatment modality for the primary tumor. Neck dissection is recommended in TUCH in all nodal positive cases, as well as in N0 cancer with a risk of occult metastasis exceeding 15%, e.g. T1 in the lower gingiva and floor of the mouth, in addition to all T2–T4 cases (16, 17). The wider use of neck dissections in the clinically negative neck has been encouraged in recent studies (18).

Radiotherapy

Radiation was delivered with a 4 to 10 MV linear accelerator using CT-assisted dose planning in all cases, since 1990. Fractionation was standard (1.8–2.0 Gy daily, 5 fractions weekly) until 1994, when accelerated hyperfractionated RT became the main regimen for treatment of the majority of the T2-4N1-3 tumors. The schedule introduced by C.C. Wang was followed, consisting of two daily 1.6 Gy fractions with a planned gap of 9 to 12 days midway through the irradiation (19). The interfraction interval was at least 6 hours. The prescribed tumor dose for curatively treated patients varied between 62 and 64 Gy as a preoperative dose, or 65 and 70 Gy in definitive radiotherapy. In individual cases, a brachytherapy boost consisting of 2–6 2–2.5 Gy fractions was used after external radiotherapy.

Of the 174 patients, 142 (82%) were treated with curative intent. Of these, 128 patients (90%) received potentially curative (>50 Gy) RT. In 34/128 (27%) cases RT was used alone, while the remaining patients had combined modality treatment, which was preoperative in 88/128 (69%) and postoperative in 6/128 (5%) cases (Fig. 1). Among these six postoperatively irradiated patients, three had cancer in the tonsil, one in the uvula, one in the oral cavity and one in the tongue.

The majority of patients were given irradiation to the primary tumor and neck using parallel or oblique opposed portals. In 94%, the portal arrangement was bilateral, and in 6% ipsilateral. Separate opposed fields were used to irradiate cervical lymph nodes in 75%, and the anterior supraclavicular field to treat the lower neck in 33% of radiated patients. In all, 27/142 (19%) had split-course accelerated hyperfractionated RT (14), while all others had standard fractionation. The median duration of RT was 45 days (range 32 to 71 days) in patients with curative intent. The median dose of external beam radiation to the primary tumor was 64 Gy, range 51 to 79 Gy. In addition, six patients received intracavitary brachytherapy using the afterload technique with a dose ranging from 4 to 15 Gy. The median dose to the neck in uninvolved nodes was 52 Gy, range 30 to 74 Gy, and to the supraclavicular area 45 Gy, range 39 to 58 Gy. The median overall treatment time in combined curatively treated patients, including the operation, was 76 days, range 55 to 126 days.

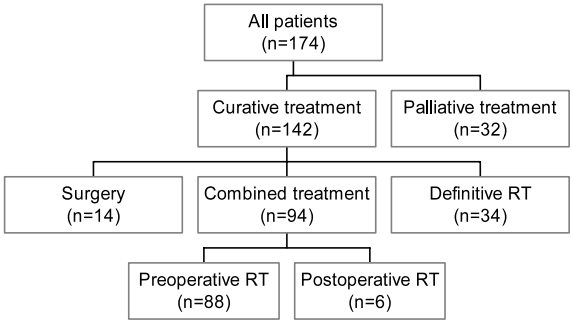

Fig. 1. Breakdown of different treatment modalities in SCC patients of the head and neck. Total number of patients receiving RT was 148, including both curative and palliative treatment.

Surgery

The diagnosis was verified in all cases with a biopsy, which in small lesions could be excisional. Early (T1, and some T2N0) tumors in the OC and OP were resected with over 10 mm margins without reconstruction or using a local flap. The surgery for advanced tumors consisted of a block resection and reconstruction with a free microvascular transfer or a pedicled musculocutaneous flap. All N positive and N0 patients at risk of occult metastases exceeding 15% were treated with neck dissection. The extent of the surgery was decided by the tumor board after preoperative examinations including panendoscopy.

Surgery as the only curative treatment was used in 14, and in combination with RT in 94 patients. The operation consisted of a local radical resection in 62, a block resection and flap reconstruction in 46 with an additional laryngectomy in eight patients. For reconstruction a local flap was used in 11 patients, a pedicled musculocutaneous flap in eight cases, while 27 patients received a free multitissue microvascular transfer.

A neck dissection was done in 77 (71%) of the 108 surgically treated patients. The neck dissections were classified according to the Official Report of the Academy's Committee for Head and Neck Surgery and Oncology (20). Of the 77 ipsilateral neck dissections performed, 9 were radical, 10 modified radical, 29 functional and 29 were supraomohyoidal. Bilateral neck dissections were done in seven (4%) cases. All contralateral neck dissections were supraomohyoidal.

In the group of 108 patients operated with curative intent, the operation was macroscopically radical in 105, unclear in one, and non-radical in two cases; the tissue margins were microscopically positive in two, uncertain in 15, and negative for cancer in 90 cases; in one case the information was not available. Tumor tissue was found in the resection after radiotherapy in 51 out of 89 cases.

No chemotherapy was used for primary cases during the study period. All patients were followed until death or for at least 5 years.

Statistics

Survival rates were estimated with the Kaplan–Meier method. We also calculated the 95% confidence interval (95% CI) and the cancer-related survival separately for all patients and for curatively treated patients. A subgroup analysis on survival was performed, e.g. in patients receiving definitive radiotherapy or surgery only and in the group receiving combined modality treatment consisting of irradiation and surgery. Computation was done with the SAS System for Windows, release 8.2/2001 SAS Institute Inc., Cary, NC, USA. The cumulative relative survival rates were calculated according to Verdecchia et al. (21) using SURV3 software (Finnish Cancer Registry, Helsinki, Finland).

RESULTS

Recurrent disease

Forty-four (31%) of the curatively treated patients (n = 142), had a recurrence (Fig. 2). In addition, the carcinoma was classified as persistent in 19/142 patients (13%), when the recurrence occurred within 3 months. Of these patients, 13 had had only definitive RT at a dose ranging from 51 Gy to 79 Gy, whereas 6 patients had undergone a combined treatment with radiotherapy and surgery. All these patients had viable cancer at the time of surgery, and 5 had positive surgical margins. Seventy-nine patients (79/142, 56%) had no recurrences.

In addition to the three patients with distant metastasis at the time of presentation and three patients with persistent disease, five curatively treated patients developed distant metastases during the follow up (Fig. 2). Of the recurrences in patients treated with irradiation, 36 were situated in the full dose area, 6 within the extended fields encompassing the 50 Gy isodose, 2 at the portal margin and 7 outside the field.

Eleven patients (6.3%) developed a second primary tumor: 1 prostate cancer, 2 breast cancers, 3 lung cancers, 1 meningioma, 2 gastrointestinal cancers, 1 mesenchymal sarcoma and 1 lingual carcinoma.

Complications

All patients developed mild to severe radiation mucositis during the treatment. Interruption of the treatment was due to mucositis in 20/148 cases (14%).

Four (2.8%) patients were reported to have osteoradionecrosis of the mandible. The tumor doses for these patients were 60–66 Gy, the maximum dose per fraction varying between 1.98 and 2.13 Gy, except for one patient who had received hyperfractionated therapy consisting of two 1.6 Gy fractions/day. Ten patients (7%) had other problems after treatment: an infection and/or necrosis of a flap and/or

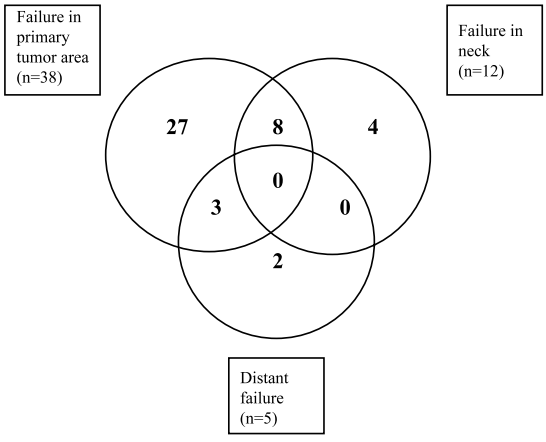

Fig. 2. Failure pattern in patients treated with curative intent (n = 142). Patients with persistent tumors have not been included.

stricture (three), fistula requiring surgery (two), myocardial infarction (one), cerebrovascular attack (one), soft tissue necrosis, fistula and pseudoarthrosis (one), death post-operatively due to subsequent surgery (one) and one patient needed suturing to the flap postoperatively. The patient with flap necrosis was operated on only, and the others were preoperatively irradiated.

Survival

The five-year relative survival rate was 40% for all 174 patients, and 43% for the 142 patients who had received treatment with curative intent. The Kaplan–Meier cause-specific survival estimate for the 174 patients was 49% (95% confidence interval, CI 41% to 57%) at 5 years, while the overall survival estimate was 32% (95% CI 25% to 38%).

The estimate of overall survival at 5 years for the 142 patients who had received curative treatment was 35% (95% CI 27% to 43%), while the cause-specific survival estimate was 55% (95% CI 46% to 54%). For the curatively treated patients, the local control at 5 years was 60% (52–68%); the disease-specific 5-year survival rate was 65% for lingual cancer patients, 45% for those with other oral tumor localizations, 64% for oropharynx patients and 47% for the patients with hypopharyngeal cancer. The 5-year survival rates by stage and by region among the curatively treated patients are shown in Figs. 3 and 4, respectively. The corresponding cause-specific estimates of survival were 26%, 61% and 70% in the irradiation, combined treatment and surgery groups, respectively. The 5-year cancer-related survival in patients treated with RT with curative intent was 53% in the group given >62 Gy, and 57% in the group given ≤ 62 Gy. There was no difference in 5-year survival between patients under or over 60 years (54% vs. 57%, NS).

DISCUSSION

The aim of the treatment is to obtain the highest cure rate and the lowest morbidity with few side effects. The current study represents a non-selected group of HNSCC patients

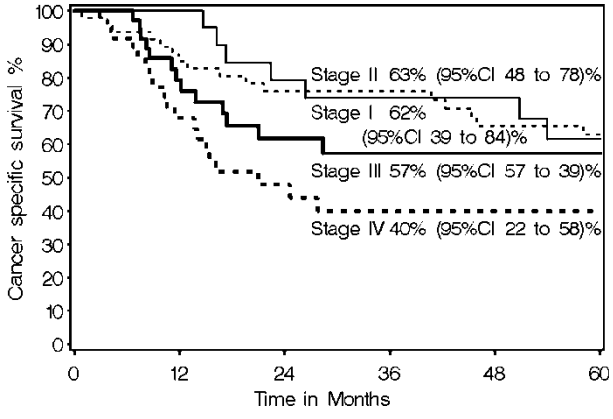

Fig. 3. The cancer-specific survival among the patients treated with curative intent (n = 142) as related to primary staging.

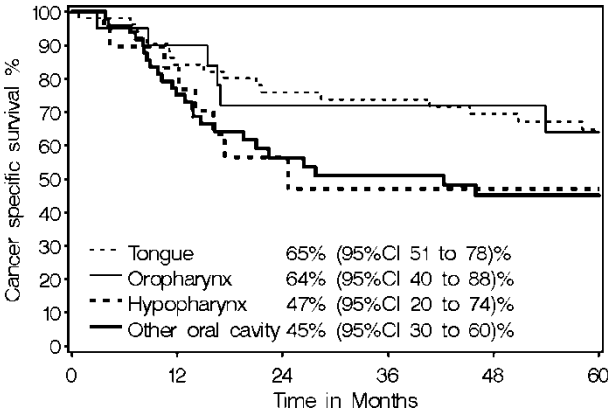

Fig. 4. The cancer-specific survival among the patients treated with curative intent (n = 142) as related to localization: the tongue, other oral cavity, oropharynx and hypopharynx.

referred from a geographically defined district to the only referral center in this area. The population is small but the importance of evaluating the treatment method used has led to the need for this kind of evaluation.

The 5-year disease-specific survival in the curatively treated group was 55%, which compares favorably with other treatment protocols (7). We have previously reported improved survival in early lingual cancer with surgery alone (15).

Head and neck cancer has traditionally been a disease dominated by the male gender. In the present study, as shown in Table 1, the male/female ratio was approximately 1:1; females predominated among the patients with cancer of the mobile tongue, whereas hypopharyngeal cancer is more common among males. This is in accordance with other recent reports (22). Interestingly, the majority (68%) of the females who reported smoking habits were non-smokers, with the highest figure among tongue cancer patients, which is the fastest increasing group in Finland (5). This supports the concept that a certain subpopulation of head and neck cancer patients lack the traditional risk factors of heavy smoking and alcohol consumption, which constituted the dominant lifestyle of patients with oro- and especially hypopharyngeal cancer.

Recurrences occurred in 44 cases (31%). In this study the disease is defined as recurrent if it recurs over 3 months after the end of the treatment, whereas some others have selected a longer period of 6 months. The most common site for recurrence was the primary site, with 27/44 (61%) recurring only in the primary site. This group could benefit from more effective locoregional treatment such as hyper-fractionated/accelerated radiotherapy or concomitant chemoradiation in combination with surgery (23).

Of the patients treated with surgery with curative intent, 75% also underwent a neck dissection. Only four (3%) of the 142 patients treated with curative intent had recurrence in the neck only, whereas 8 (6%) patients had recurrence both in the neck and in the primary site. It has been

reported earlier in a study consisting of 95 patients with primary neck nodes treated with RT and neck dissection that 26% recurred in the regional neck nodes during the follow-up period (24). In a Swedish study of early Stage I tongue cancers treated with surgery of the primary tumor 14 of 58 patients had recurrences in the neck region with a mean follow-up time of 33 months (25). In another study among early tongue carcinoma patients, the recurrence rate after elective neck dissection vs. observation was 9% and 47%, respectively (17). Thus, active treatment of the neck seems warranted (26, 27). During follow up, only two of the patients treated with curative intent presented with distant metastases as the only site of disease (Fig. 2). This shows that the control of the loco-regional tumor is the cornerstone in the treatment of HN cancer.

Secondary primary tumors were diagnosed in 11 patients (6.3%), which seems to be a low number in comparison with other reports (28).

An expected complication from other studies among patients treated with irradiation (dose range 60–66 Gy) was osteoradionecrosis (2.8%); the other major complications occurred in 7% among the patients treated with curative intent including surgery (29, 30).

The median overall treatment time was 76 days in the patients receiving combined modality treatment with preoperative radiotherapy. The treatment time is shorter compared with that usually reported with postoperative radiotherapy. Recently, Ang et al. (31) reported that the overall treatment time of combined therapy significantly affects locoregional control and survival, suggesting that our approach may be beneficial.

Preoperative radiotherapy is known to reduce local recurrence and potential distant metastases. On the other hand, difficulties in determining the extent of the tumor and the delay before surgery, in addition to complications due to preoperative radiotherapy, cause concern (32). Therefore, meticulous clinical examination, including panendoscopy and bimanual palpation of the tumor site, is mandatory, in addition to adequate imaging.

We conclude that preoperative radiotherapy is a feasible treatment schedule for squamous cell carcinoma of the head and neck located in the oral cavity, oropharynx and hypopharynx. The morbidity associated with surgery can be controlled by limiting the time between radiotherapy and operation to 3–5 weeks and keeping the patients under surveillance during the first 5 years after treatment. The prognostic and predictive factors for the selection of the best treatment for each patient will be the main focus of our future research.

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REFERENCES

1. Teppo H, Koivunen P, Sipilä S, et al. Decreasing incidence and improved survival of laryngeal cancer in Finland. Acta Oncol 2001; 40: 791–5.
2. Raitiola HS, Pukander JS. Changing trends in the incidence of laryngeal cancer. Acta Oncol 1997; 36: 33–6.
3. Raitiola H, Pukander J. Symptoms of laryngeal carcinoma and their prognostic significance. Acta Oncol 2000; 39: 213–6.
4. Virtaniemi JA, Hirvikoski PP, Kumpulainen EJ, et al. Is the subsite distribution of laryngeal cancer related to smoking habits? Acta Oncol 2000; 39: 77–9.
5. Finnish Cancer Registry. Annual Reports. Cancer Incidence in Finland 1968–1997. Helsinki: Finnish Cancer Registry, Helsinki, 1971–2000.
6. Dickman PW, Hakulinen T, Luostarinen T, et al. Survival of cancer patients in Finland 1955–1994. Acta Oncol 1999; 38(Suppl 49): 1–103.
7. Parsons JT, Mendenhall WM, Stringer SP, et al. Squamous cell carcinoma of the oropharynx—surgery, radiation, or both. Cancer 2002; 11: 2967–80.
8. Bhattacharyya N. The effects of more conservative neck dissections and radiotherapy on nodal yields from the neck. Arch Otolaryngol Head Neck Surg 1998; 124: 412–6.
9. Bengtson GP, Schusterman MA, Baldwin BJ, et al. Influence of prior radiotherapy on the development of postoperative complications and success of free tissue transfers in head and neck cancer reconstruction. Am J Surgery 1993; 166: 326–30.
10. Cummings CW, Fredricsson JM, Harker LE, Krause CJ, Richardson MA, Schuller DE. Otolaryngology—head and neck surgery, 3d ed. Missouri: Mosby Year Book, St Louis; 1998.
11. Wratten CR, Puolsen MG, Williamson S, et al. Effect of surgery on normal tissue toxicity in patients treated with accelerated radiotherapy. Acta Oncol 2002; 41: 56–62.
12. Sobin LH, Wittekind Ch. TNM Atlas. Illustrated guide to the TNM/pTNM classification of malignant tumours. 3rd ed, 2nd revision. New York, Berlin, Heidelberg: Springer-Verlag; 1992.
13. Zubrod GG. Appraisal of methods for the study of chemotherapy of cancer in man: comparative therapeutic trial of nitrogen mustard and triethylene thiophosphamide. J Chron Dis 1960; 11: 7–33.
14. Histological typing of tumours of the upper respiratory tract and ear. International histological classification of tumours. World Health Organization. Berlin: Springer Verlag; 1991.
15. Luukkaa M, Aitasalo K, Pulkkinen J, et al. Neodymium YAG contact laser in the treatment of cancer in mobile tongue. Acta Otolaryngol 2002; 122: 318–22.
16. Kramer D, Durham JS, Jackson S, et al. Management of the neck in N0 squamous cell carcinoma of the oral cavity. J Otolaryngol 2001; 30: 283–8.
17. Haddadin KJ, Soutar DS, Oliver RJ, Webster MH, Robertson AG, MacDonald DG. Improved survival for patients with clinically T1/T2, N0 tongue tumors undergoing a prophylactic neck dissection. Head Neck 1999; 21: 517–25.
18. Dias FL, Klingerman J, Matos de Sa G, et al. Elective neck dissection versus observation in stage I squamous cell carcinomas of the tongue and floor of the mouth. Otolaryngol Head Neck Surg 2001; 125: 23–9.
19. Wang CC. Radiation therapy for head and neck neoplasms, 3rd ed. New York: Wiley-Liss; 1997. p. 124–36.

20. Robbins KT, Medina JE, Wolfe GT, Levine PA, Sessions RB, Pruet CW. Standardizing neck dissection terminology, official report of the Academy's Committee for Head and Neck Surgery and Oncology. Arch Otolaryngol Head Neck Surg 1991; 117: 601–5.
21. Verdecchia A, Capocaccia M, Santaquilani M, Hakulinen T. Methods of survival data analysis and presentation issues. In: Berrino F, Capocaccia R, Esteve J, et al., eds. Survival of cancer patients in Europe: the EUROCARE-2 Study. Lyon: IARC Scientific Publications 1999; 151: 41–5.
22. Annertz K, Anderson H, Biorklund A, et al. Incidence and survival of squamous cell carcinoma of the tongue in Scandinavia, with special reference to young adults. Int J Cancer 2002; 101: 95–9.
23. Stuschke M, Thames HD. Hyperfractionated radiotherapy of human tumors: overview of the randomized clinical trials. Int J Radiation Oncol Biol Phys 1997; 37: 259–67.
24. Lundahn RE, Foote RL, Bonner JA, et al. Combined neck dissection and postoperative radiation therapy in the management of the high-risk neck: matched-pair analysis. Int J Radiat Oncol Biol Phys 1998; 40: 529–34.
25. Nathanson A, Ågren K, Biörklund A, et al. Evaluation of some prognostic factors in small squamous cell carcinoma of the mobile tongue: a multicenter study in Sweden. Head Neck 1989; 11: 387–92.
26. Vermund H, Boysen M, Evensen JF, et al. Recurrence after different primary treatment for cancer of the supraglottic larynx. Acta Oncol 1998; 37: 167–73.
27. Jakobsen J, Hansen O, Jorgensen KE, et al. Lymph node metastases from laryngeal and pharyngeal carcinomas—calculation of burden of metastasis and its impact on prognosis. Acta Oncol 1998; 37: 489–93.
28. León X, Quer M, Diez S, et al. Second neoplasm in patients with head and neck cancer. Head Neck 1999; 21: 204–10.
29. Glanzmann C, Grätz KW. Radionecrosis of the mandibula: a retrospective analysis of the incidence and risk factors. Radiother Oncol 1995; 36: 94–100.
30. Kramer S, Gelber RD, Snow JB, et al. Combined radiation therapy and surgery in the management of advanced head and neck cancer: final report of study 73-03 of the Radiation Therapy Oncology Group. Head Neck Surg 1987; 10: 19–30.
31. Ang KK, Trotti A, Brown BW, et al. randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 2001; 51: 571–8.
32. Perez C A, Brady L W. Principles and practice of radiation oncology, 3rd ed. Philadelphia, New York: Lippincott-Raven; 1998. p. 981–1068.