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Nodal Control and Surgical Salvage after Primary Radiotherapy in 1 782 Patients with Laryngeal and Pharyngeal Carcinoma

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The purpose of this study was to evaluate the ultimate neck control after primary radiotherapy and surgical salvage in laryngeal and pharyngeal cancer patients. Some 1 782 consecutive patients with squamous cell carcinoma were treated by radiotherapy. At presentation 26% of the patients had metastatic lymph nodes. A total of 298 primary or secondary nodal recurrences were seen, 159 were treated, and 53 (53/298 ~18%) were controlled. Isolated N-recurrence was fatal in 2.7% (36/1 324) of the N0 patients. Univariate actuarial analysis of nodal control demonstrated that the region of origin, T-classification, T-size, N-classification, tumor stage, differentiation, hemoglobin, and radiation time were significant prognostic factors. In a Cox analysis the independent significant parameters were gender, region of origin, N-classification, and differentiation. The conclusions were that in patients with nodal recurrence a little over half were treated and of these a third of the nodal recurrences were controlled. Significant prognostic factors in multivariate analysis were gender, region of origin, N-classification, and tumor differentiation.

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The treatment strategy in Denmark for patients with laryngeal and pharyngeal carcinoma, and also at our institution, has been organ-preserving primary radiotherapy, reserving surgery for recurrences. In previous publications on supraglottic carcinoma (1), glottic carcinoma (2), prognostic factors in laryngeal carcinoma (3), nasopharyngeal carcinoma (4), oropharyngeal carcinoma (5), and hypopharyngeal carcinoma (6) we have described the primary radiation treatment, recurrence pattern including salvage surgery, and prognostic factors in patients with laryngeal and pharyngeal carcinoma.

The present publication is focused on neck-node control and the surgical management of nodal recurrences in laryngeal and pharyngeal cancer patients treated with primary radiotherapy. This series include all consecutive patients with squamous cell carcinoma. All had primary radical radiotherapy and there was no referral bias.

MATERIAL AND METHODS

Between January 1963 and December 1991, 1 874 patients with squamous cell carcinoma of the larynx or pharynx were referred to the head and neck oncology team at Aarhus University Hospital. The institution receives all patients from an area with approximately 1 million inhabitants. The present analysis includes the 95% (1 782/1 874) of the patients in whom the treatment was primary radical intended radiotherapy (34 patients for various reasons had primary curatively intended surgery and 58 did not have curative treatment). Some patients (40) included in the present analysis did not receive a curative dose of radiotherapy, as for different reasons (concurrent disease, age, refusal, death) they did not complete the scheduled treatment.

The regions of origin were the supraglottic larynx 22% (394 pts), glottic larynx 47% (834 pts), subglottic larynx 1% (22 pts), nasopharynx 8% (145 pts), oropharynx 15% (267 pts), and hypopharynx 7% (120 pts). Twenty per cent (352/1782) of the patients were females and 80% (1430/1782) were males. The median age was 63 years (range 17–93 years). All patients had biopsy-proven squamous cell carcinoma. The histological grading of the tumor was recorded in 88% (1572/1782) of the patients; 35% (555/1572) were well, 30% (464/1572) moderately, and 35% (553/1572) poorly differentiated. At presentation 26%

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(458/1782) of the patients had metastatic lymph nodes, with the ipsilateral sub-digastric and mid-jugular nodes most often involved. All patients were classified or re-classified according to the UICC 1982 classification (7) and the distribution is given in Table I. Consequently 37% were in stage I, 21% in stage II, 24% in stage III, and 18% in stage IV. Before the start of treatment the patient was assessed by both a specialist in oncology and an ENT specialist including assessment and biopsy under general anesthesia. The standard radical radiotherapy technique was parallel opposed fields using cobolt-60, or 4–6 MV photons (last part of the study period). The primary target included the tumour and the regional lymph nodes. For radiotherapy technique details related to the different anatomical regions, please consult previous publications (1, 2, 4–6).

Patients were followed at the University Hospital for a period of at least 5 years after treatment, with a joint evaluation by specialists in head and neck surgery and in radiation oncology. The scheduled visits were: year 1+2 every 3 months, year 3 every 4 months, year 4 every 6 months, and the last follow-up visit after minimum 5 years. Patients in the early part of the study period were seen every year up to 10 years. Disease status was routinely documented in the patient chart, and for the present analysis all charts were reviewed. The survival status of all patients was updated as at 1 September 2000 using the Central Population Registry and the National Cancer Registry. Data were recorded in a Medlog® database and SPSS® computer software was used in the analysis. The clinical endpoints used for neck nodes (N) were persistent control of the neck after primary treatment with or without salvage treatment. 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 hazard model. Parameters were included in the model using forward selection, and the level of significance was selected to 5%.

Table I

(A): The TNM classification for 1 782 patients with laryngeal and pharyngeal squamous cell carcinoma treated with primary radiotherapy (UICC 1982)

	N0	N1	N2	N3	Total	
T1	653	66	12	34	765	(43%)
T2	373	71	19	29	492	(28%)
T3	219	77	15	50	361	(20%)
T4	79	33	14	38	164	(9%)
	1 324	247	60	151	1 782	(100%)

No patients with distant metastases.

RESULTS

The pattern of first failure is illustrated in Fig. 1. Of the 257 patients with nodal recurrence, 220 patients were candidates for salvage treatment (123 who had an isolated N recurrence and the 97 who had a combined TN recurrence). In the remaining 37 patients an M recurrence was diagnosed and thereby these patients could not be offered curative salvage treatment. In the N0 patient group the number of nodal metastases was 93; in 8 patients a distant (M) metastasis was found, meaning that the frequency of patients with nodal metastases that were candidates for loco-regional salvage was 6% (85/1324). In other words, 85/220 (39%) of the first recurrences developed in N0 patients. The remaining 135/220 (61%) patients with nodal recurrence or persistent disease evaluated for salvage treatment were part of the 458 patients with initial N+ disease (29%). For details see Table II. The corresponding figures for second recurrence are also seen in Table II. It should be noted that a second nodal recurrence can also be found in a patient with an isolated T recurrence without previous neck failure and that the patients at risk are those with a recurrence and an intended curative recurrence treatment (468 patients). Table II also shows that the nodal recurrence rate in the N0 patients is 6% at first recurrence and 14% at second recurrence. Likewise, if the patient had nodal metastases before treatment (N+) the frequency was at the same level: 29% (135/458) at first recurrence as compared with 27% (29/107) at second recurrence. It is also seen that combined T+N recurrences make up 44% (97/220) of first recurrences, but only 9% (7/78) of second recurrences (Table II).

(B): The TNM classification and incorporated 220 primary N recurrences or N+T recurrences for each TN class

	N0	N rec.	N+T rec.	N1	N rec.	N+T rec.	N2	N rec.	N+T rec.	N3	N rec.	N+T rec.	Total	N rec.	N+T rec.
T1	653	21	9	66	12	3	12	2	3	34	8	3	765	43	18
T2	373	18	9	71	14	6	19	1	3	29	3	3	492	36	21
T3	219	9	9	77	9	15	15	3	3	50	9	11	361	30	38
T4	79	7	3	33	1	6	14	1	1	38	5	10	164	14	20
	1 324	55	30	247	36	30	60	7	10	151	25	27	1 782	123	97

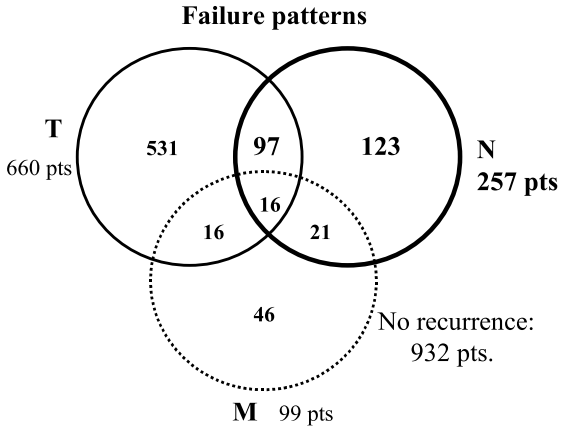

Fig. 1. Failure patterns in 850 of 1 782 patients treated with curative intention for laryngeal and pharyngeal carcinoma. In 932 patients no recurrence was seen.

If we look at the first nodal recurrence and break down the recurrence frequency into three equal time periods (9Y+8M) we observe that the number of patients increases but the actuarial 5-year nodal recurrence risk was almost unaltered. The three periods involved 505 patients with a risk of 14±2%, 595 patients with a risk of 11±1%, and 682 patients with a risk of 16±2% (n.s.). The breakdown was also made for three treatment policies; one with continuous treatment 57–61 Gy/30 fx/5 fx per wk comprising 855 patients, one with split course treatment, typical 40 Gy/20 fx—3 wk split—26–32 Gy/13–16 fx comprising 497 patients, and one with continuous treatment 62–68 Gy/30–34 fx/5 fx per wk comprising 431 patients. Also here the nodal recurrence rate was almost the same with 12±1%, 14±2%, and 16±2% (n.s.).

In Table III is demonstrated the number of patients with a recurrence, the numbers treated and the numbers controlled. Regarding the first recurrence, it is shown that 19% (43/220) of the patients with recurrence were controlled. This finding is also demonstrated in Fig. 2 (observe that the figures are actuarial, that one of the events is after 10 years and that the 43 events represent the difference between the two curves). If only the N0 patients were considered, the control rate was 29% (25/85). The corresponding rate for the N+ patients was 13% (18/135). This is demonstrated in Fig. 3. An interesting subgroup of the 1 324 N0 patients comprised 55 who had an *isolated* N-recurrence. Of these 37 were treated and 19 were controlled, but in 36/1 324 (2.7%) of the patients with isolated nodal metastases the disease was fatal. By the second recurrence the figures are too small for any reasonable comparison. We have looked at the location of the metastatic nodes in relation to the primary radiation field. A total of 298 primary or secondary recurrences were seen and in 238/298 (80%) the relevant information was available. A metastatic node inside or at the border of the radiation field was seen in 206/238 (87%) and only in 32/238 (13%) was the metastatic node definitely outside the field. Of the recurrences outside the radiation field 13 were in N0 patients, 15 in N1, and four in N3 patients. Five different anatomical regions of origin were represented (– subglottic); the factors notable was that 12/32 (38%) patients initially had a supraglottic and 7/32 (22%) a nasopharyngeal carcinoma.

The distribution of recurrent metastatic lymph nodes, per level, by the first or second recurrence is demonstrated in Fig. 4. The information was available in 275/298 (92%) of the recurrences, and a maximum four node groups were recorded per patient. The treatment choice for nodal recurrence with curative intention was predominantly neck dissection, with modifications of the classic radical neck dissection and variations in dissected levels according to the location and extent of the metastatic nodes. In total 139 patients with first and/or second recurrence had a neck dissection (in some combined with laryngectomy), 5 had additional irradiation, and 2 had chemotherapy; 34% were controlled. An isolated nodal recurrence was seen in 194 patients by the first or second recurrence; 99 had a nodal dissection and 40 were controlled (40%). In the group with combined local and nodal recurrence there were 104 patients; 43 had a nodal dissection, most often combined with a laryngectomy, and only 9 (21%) were controlled. Eighteen with nodes outside the primary irradiated field were treated by radiotherapy, in 3 chemotherapy was added; 33% were controlled. Two had chemotherapy alone and

Table II

N and T+N recurrences related to nodal status before first treatment

1. Recurrence		N0 (1324 pts)	N+ (458 pts)	All (1782 pts)
	N recurrence	55	68	123
	T+N recurrence	30	67	97
	All	85/1 324 (6%)	135/458 (29%)	220/1 782 (12%)
2. Recurrence		N0 (361 pts)	N+ (107 pts)	All (468 pts)
	N–recurrence	46	25	71
	T+N recurrence	3	4	7
	All	49/361 (14%)	29/107 (27%)	78/468 (17%)

Table III

Number of N and T+N recurrences, number of patients treated and number controlled

Recurrence		Number	Treated	Controlled
1	N recurrence	123	84	34
	T+N recurrence	97	42	9
	All	220	126	43 (43/220 ~19%)
2	N recurrence	71	32	10
	T+N recurrence	7	1	0
	All	78	33	10 (10/78 ~13%)
1+2	All	298	159	53 (53/298 ~18%)

were not controlled. Palliative treatment was offered in 55 patients, most often in the form of radiotherapy and/or chemotherapy.

Univariate actuarial nodal controls after primary treatment and after recurrence treatment for selected parameters in the 1 782 patients are listed in Table IV. The results are 5-year values for number of events and percentages. Patient gender and age did not influence the nodal control. The region of origin was highly significant with the best prognosis seen for glottic tumors. T classification, T size, N classification, tumor stage, differentiation, hemoglobin, and radiation time were significant for both end-points.

The Cox proportional hazards model for independent significant parameters was used to analyze the material for the endpoints neck failure after primary treatment and after applied recurrence treatment (Table V). The analysis included 1 570 patients in whom all parameters were available. The final model showed that significant independent prognostic parameters were gender, region of origin, N classification, and differentiation. Surprisingly, T classification was not an independent significant parameter. A Cox analysis stratified for N0 alone and for N1–3 did not give any additional information.

DISCUSSION

In this paper on nodal metastases we have shown that only a few of the patients (6%) with clinical N0 disease at initial treatment experienced a neck recurrence (some combined with a T recurrence) after primary treatment. An interesting subgroup was 55 patients who had an *isolated* N recurrence of whom 36 died as a consequence of the nodal recurrence. In contrast with this, patients with primary N+ disease developed nodal metastases as first recurrence in 29% of cases. If a further breakdown was made of treatment period

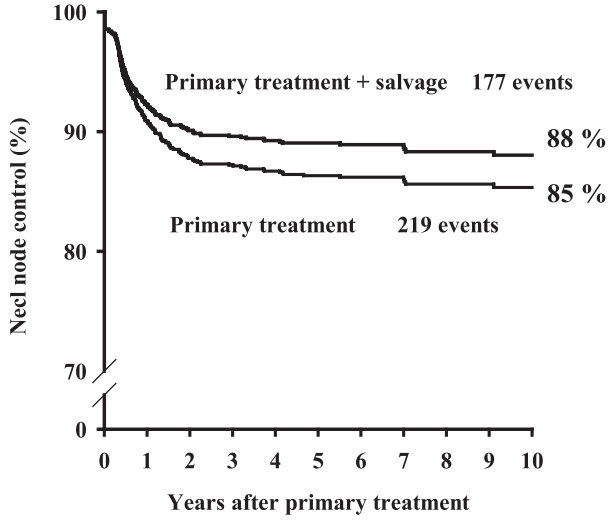

Fig. 2. Neck node control in 1 782 laryngeal and pharyngeal carcinoma patients. The lower curve shows the result of the primary curatively intended treatment with 219 events. The upper curve shows the result after salvage treatment; only 177 events due to successful salvage. Observe scaling of Y axis.

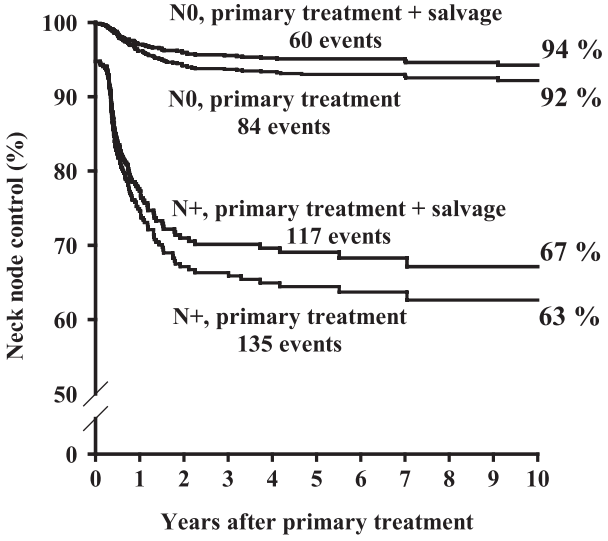

Fig. 3. Neck node control in 1 324 N0 and 458 N+ laryngeal and pharyngeal carcinoma patients. The lower of the curve pairs shows the result of the primary curatively intended treatment. The upper shows the result after salvage treatment. Observe scaling of Y axis.

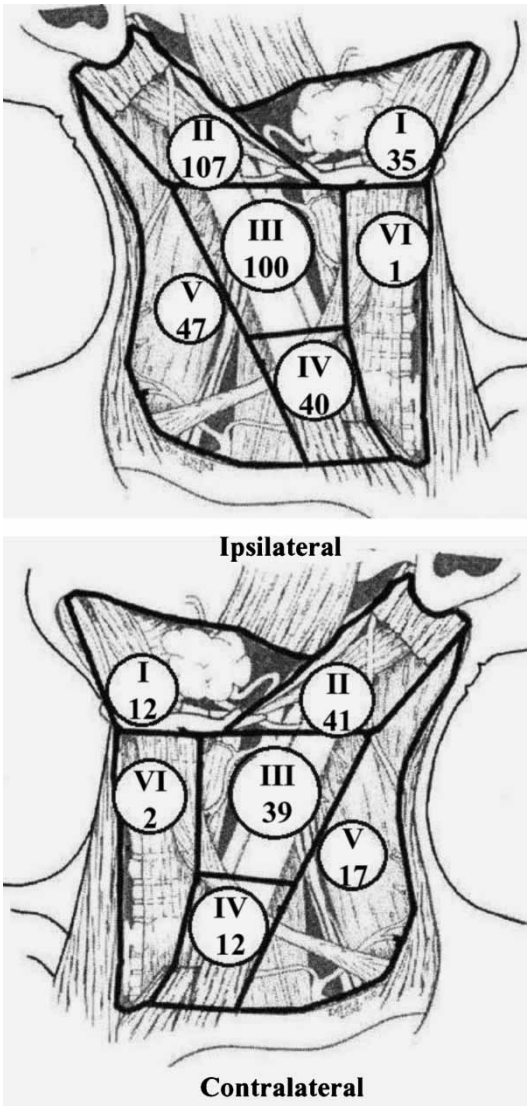

Fig. 4. Distribution of recurrent metastatic lymph nodes per level. In total 275 patients with primary or secondary nodal recurrences (information in 275/298 ~92% of the recurrences); maximum four node groups per patient.

and nodal classification, no trend was seen over the treatment periods.

In other materials on head and neck carcinoma patients the included regions differ and—also therefore—the frequency of nodal recurrences varies. In material by Jones et al. using radical radiotherapy for squamous cell carcinoma of the larynx, oropharynx, and hypopharynx the primary actuarial nodal recurrence risk was 24% at 5 years (8). In their material comprising 1 085 patients, 50% were T1 and 80% were N0 (our figures were 43% and 74% respectively). Our primary actuarial nodal control was 86% at 5 years. In material by Mendenhall et al. on 400 carcinomas of the tonsillar region treated by radiotherapy, where approximately one-third underwent planned neck dissection, the 5-year neck control was 85% (9). In our material on oropharyngeal carcinoma all treated by radiotherapy the 5-year neck control was 60% (5). Mendenhall (10) listed the 10-year results for Aarhus (1) vs. the University of Florida (11) as follows: loco-regional control, 40% vs. 68%; cause-specific survival, 58% vs. 67%; but absolute survival, 33% vs. 27%. It was argued that, "a more aggressive fractionation schedule results in a higher likelihood of loco-regional control and a modest improvement in cause-specific survival. However, there is no significant difference in overall survival between the two groups of patients." It should also be noted that in our series no selection has taken place.

Chan et al. followed up patients with supraglottic carcinoma treated by primary radical radiotherapy (12). They concluded that in patients with complete response, 4–6 weeks after definitive radiotherapy, in whom post-radiotherapy neck dissection was withheld, the regional control rates were 75% and 86% for N1 and N2, respectively. It was also noted that a relapse in both the primary and the regional sites was the most common pattern of failure. In our material (Table IB) there was a dominance of isolated N recurrence compared with T+N recurrences in the earlier stages, but we have the same findings in the more advanced stages. Wax and Touma studied recurrent N0 laryngeal carcinoma patients after radiotherapy (13). They examined the incidence of subclinical metastatic disease in patients undergoing elective neck dissections with salvage laryngectomy. The conclusion was that although the neck was clinically negative, subclinical cervical metastases were often present. Morbidity of a neck dissection is minimal, with a high probability of control of the neck, and they advocate this therapy.

Analysis of the location of the recurrent nodes, relative to the radiation field, demonstrated that only relatively few (13%) of the recurrences were outside the field, and a single cause of these recurrences out of field could not be demonstrated. The number of recurrences within the field suggests that the intensity of radiation to the tumor must have been insufficient to eradicate the disease. In this line of argumentation it could be argued that surgery should be employed in the primary treatment. However, the frequency of secondary nodal metastases in the present material is at the same level as in treatment regimens where radical node dissection has been an integrated part of primary treatment, although the management can rarely be compared as, for example, the patients with N3 disease are often excluded in the surgical regimens (14, 15). Monotherapy has been used systematically in our material with primary radiotherapy and surgical salvage in the case of recurrence. As demonstrated in our material, the results may have been acceptable in N0 patients, but not in the N1–3 patients. This finding was also emphasized by a recent DAHANCA study on shortened treatment time, where the significant benefit of acceleration was seen only for primary tumor control, but

Table IV

Univariate actuarial analysis of nodal control in 1 782 patients with laryngeal and pharyngeal squamous cell carcinoma. The listed events are 5-year values and the percentages are 5-year Kaplan–Meier estimates ± SE. Significant differences (1% level) shown in bold

Parameter	No.	N control after primary treatment		N control after salvage treatment	
		Events	%	Events	%
All patients	1 782	214	86 ± 1	172	89 ± 1
Female	352	45	86 ± 2	35	89 ± 2
Male	1 430	169	87 ± 1	137	89 ± 1
Age 18–65	984	122	87 ± 1	93	90 ± 1
65+	798	92	86 ± 1	79	88 ± 1
Glottic (+subgl.)	856	**34**	**96 ± 1**	**27**	**97 ± 1**
Supraglottic	394	**66**	**81 ± 2**	**53**	**85 ± 2**
Nasopharynx	145	**24**	**79 ± 4**	**18**	**84 ± 4**
Oropharynx	267	**52**	**75 ± 3**	**40**	**81 ± 3**
Hypopharynx	120	**38**	**59 ± 6**	**34**	**63 ± 6**
T1	765	**57**	**92 ± 1**	**43**	**94 ± 1**
T2	492	**57**	**86 ± 2**	**40**	**90 ± 1**
T3	361	**66**	**78 ± 2**	**57**	**82 ± 2**
T4	164	**34**	**73 ± 4**	**32**	**75 ± 4**
N0	1324	**81**	**93 ± 1**	**57**	**95 ± 1**
N1	247	**65**	**68 ± 3**	**53**	**73 ± 3**
N2	60	**17**	**68 ± 7**	**17**	**68 ± 7**
N3	151	**51**	**56 ± 5**	**45**	**62 ± 5**
Stage I	653	**27**	**95 ± 1**	**18**	**97 ± 1**
Stage II	373	**27**	**92 ± 2**	**18**	**94 ± 1**
Stage III	433	**75**	**79 ± 2**	**58**	**84 ± 2**
Stage IV	323	**85**	**67 ± 3**	**78**	**70 ± 3**
Well differentiated	555	**31**	**94 ± 1**	**25**	**95 ± 1**
Mod. differentiated	464	**50**	**88 ± 2**	**37**	**91 ± 1**
Poorly differentiated	553	**102**	**78 ± 2**	**88**	**81 ± 2**
High hemoglobin[1]	871	**96**	**88 ± 1**	**72**	**91 ± 1**
Low hemoglobin[1]	755	**109**	**83 ± 2**	**93**	**86 ± 1**

[1]High hemoglobin: women $\geq$8.0 mmol/l; men $\geq$9.0 mmol/l.

was non-significant for neck-node control (16). In the future the solution may be planned combined therapy, starting with radiotherapy and followed by neck dissection and /or chemoradiotherapy in patients with a large nodal burden (N2–3). Morbidity of neck dissection seems to be a minor problem, especially if the surgery is timed to be approximately 6 weeks after completed radiotherapy (also allowing sufficient time to evaluate the full effect of the radiotherapy). In a literature review on planned neck dissection after definitive radiotherapy for head and neck carcinoma it was stated that patients with N1 disease and complete response could be observed (17). In N2–3 patients, neck dissection after definitive radiotherapy improves regional control and possibly cause-specific survival. If complete clinical and radiographic regional response is obtained observation should be sufficient. If an unclear response is obtained, it is advisable to proceed with neck dissection, as the success of salvage of an isolated recurrence in the neck is remote. Roy et al., in material comprising oropharyngeal carcinomas, made a decision prior to radiotherapy that the patient should be treated by nodal dissection no matter what the outcome of the primary treatment (18). They found that "a negative CT and clinical examination are limited in predicting a complete response. These data lend support to the role of planned neck dissection after radiotherapy of N2 neck disease." Wang et al. describe having found that 36% of patients with a complete clinical response to radiotherapy had positive nodes on histological examination (19). They found that clinical assessment after radiotherapy could not ensure the absence of neck disease. They explain, "Until there are reliable methods to distinguish which patients are truly free of neck disease, we believe the benefits of planned neck dissection outweigh the low morbidity of this procedure". Narayan et al. studied patients with advanced head and neck disease and concluded that planned post-irradiation neck dissection "provides excellent regional control and appears to cure a subset of patients" (20). On the other hand they also state that routine neck dissection adds significant morbidity and recommend observing patients who have a complete response to radiotherapy. They propose PET scanning as a way to identify patients with residual viable disease who

Table V

Cox proportional hazard analysis of prognostic factors for treatment outcome in 1 782 patients with laryngeal or pharyngeal squamous cell carcinoma treated with radical radiotherapy. The analysis included 1 570 patients for whom all listed parameters were available; the enter method was used. RR = relative risk. Significance level of 5% shown in bold

COX		N failure after primary treatment (187 events)		N failure after salvage treatment (153 events)	
Variable	Number	p-value	RR (95% CI)	p-value	RR (95% CI)
Gender					
Female	296		1.0		1.0
Male	1274	**0.008**	**1.7 (1.1–2.4)**	**0.01**	**1.7 (1.1–2.6)**
Regions					
Glottic	802	**<0.000**	1.0	**<0.000**	1.0
Supraglottic	364	**<0.000**	**2.4 (1.5–3.8)**	**0.005**	**2.1 (1.3–3.5)**
Nasopharynx	142	0.67	0.7	0.19	0.6
Oropharynx	179	**0.003**	**2.3 (1.3–4.0)**	**0.03**	**2.0 (1.1–3.6)**
Hypopharynx	83	**<0.000**	**4.2 (2.4–7.6)**	**<0.000**	**3.8 (2.0–7.2)**
N classification					
N0	1187	**<0.000**	1.0	**<0.000**	1.0
N1	200	**<0.000**	**3.9 (2.5–5.9)**	**<0.000**	**4.7 (2.9–7.7)**
N2	55	**<0.000**	**4.4 (2.5–7.8)**	**<0.000**	**6.4 (3.5–11.8)**
N3	128	**<0.000**	**7.4 (4.6–11.7)**	**<0.000**	**9.2 (5.5–15.5)**
Differentiation					
Well	555	**0.03**	1.0	**0.02**	1.0
Moderate	463	0.17	1.4	0.38	1.3
Poor	552	**0.009**	**1.8 (1.2–2.7)**	**0.009**	**1.9 (1.2–3.1)**

would benefit from neck dissection. In data from Newkirk et al. it was concluded that for patients undergoing planned neck dissection after organ preservation therapy, neck control was obtained in almost all cases (21). They also state that positive nodes may have implications for the incidence of local recurrence. In an article by Su et al. on oropharyngeal cancers it was recommended that primary radiotherapy with neck dissection should be reserved for those without complete clinical response (22). The post-irradiation surgery was without problems. Boyd et al. found that only one of 28 post-radiotherapy neck dissections identified tumor outside the nodal levels II–IV (23). They also stated that two-thirds of the dissections demonstrated no evidence of residual tumor, but without a direct correlation between pre-treatment nodal size, radiation dose delivered, and the likelihood of achieving a cancer-free neck dissection.

Combined chemoradiotherapy may be another way to intensify the treatment (24–28). A meta-analysis on chemotherapy in the treatment of head and neck squamous cell carcinoma with over 10 000 patients concluded that there was a small statistically significant benefit to survival (7–8%) when multiagent chemotherapy was added concomitantly to loco-regional treatment, but that the routine use of chemotherapy remains debatable with only a small benefit (29). Another meta-analysis on randomized trials concluded that platinum-based regimens significantly improved survival in locally advanced squamous cell head and neck cancer (30). Acute and in particular late effects have to be evaluated in well-designed prospective trials; to preserve the anatomical structures is not reasonable if late effects such as mucosal injury and fibrosis hinder normal function after an otherwise successful treatment. An analysis by Milas et al. concluded that concurrent chemoradiotherapy in terms of both loco-regional control and overall survival has emerged as an effective treatment for advanced cancer, but at the expense of a considerable increase in normal tissue toxicity (31). There are a number of potential emerging treatment strategies to further develop chemoradiotherapy and they point to improvements such as newer chemotherapeutic drugs that are enhancers of tumor radio response or selective inhibitors of epidermal growth factor receptor or cyclooxygenase-2 enzyme. The larynx preservation trials on advanced laryngeal disease compared radical surgery plus postoperative radiotherapy with neoadjuvant chemotherapy plus definitive radiotherapy. The first study was from the Veterans Affairs Laryngeal Cancer Study Group (32) and later came related studies from other groups (33, 34). Recently such an analysis of laryngeal stage III and "small" IV was presented (35). The conclusion was that in patients with laryngeal cancer, radiotherapy with concurrent administration of cisplatin is superior to induction chemotherapy followed by radiotherapy or radiotherapy alone for laryngeal preservation and locoregional control. Distant metastases were also suppressed by the treatment. Overall survival was found to be equal in the three groups.

Chemotherapy-based regimens did have greater normal tissue toxic effect. If neck dissection is applied, both in the initial treatment and in the recurrence treatment, the classification system developed for these procedures by the American Academy of Otolaryngology Head and Neck Surgery, to eliminate potential misinterpretation, should be used (36, 37). In order to describe the extent of the dissection the "level" system is used. Adherence to the principles of this classification system to describe neck dissection techniques should provide an improved method of communication. In our material the patients have most often had modified radical neck dissection.

These principles of surgical lymph node levels have also been adapted by Grégoire et al. to lymph node target volumes in radiotherapy, and here used for three-dimensional treatment planning (38). In the last few years a new technique, which could help in nodal dissection, has been developed. The "sentinel node" philosophy adopted primarily from the breast cancer—and malignant melanoma—surgery has been modified to dissection of the neck. Clinical trials and discussion are still going on, trying to document whether this regimen should be adopted as part of the standard treatment. As pointed out by several authors (36, 39–41) many problems exist with the technique that was proposed as a minimally invasive, low-morbidity modality of lymph node status assessment (42). One problem is if intraoperative examination frozen section analysis underestimates the true incidence of positive nodes and another problem could be tumor cells escaping the first draining "sentinel" lymph node.

In conclusion, the current analysis has demonstrated the following risk factors: male gender, N stage, poor differentiation, and primary tumor in oro- or hypopharynx or supraglottic larynx. The data also demonstrate that relatively few nodal recurrences can be treated with successful salvage surgery. To improve outcome in these patients, modified initial treatment introducing concurrent chemoradiation, early detection of a nodal recurrence, and a more aggressive salvage approach may be warranted.

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