CHAPTER 5

Control of nodal metastases in squamous cell head and neck cancer treated by radiation therapy or chemoradiation

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Radiother Oncol. 2006 Apr;79(1):39-44

Abstract

Background and purpose: In the present study, prognostic values of several CT-based pre-treatment nodal and treatment-related characteristics were evaluated among patients with squamous cell head and neck cancer treated with non-surgical modalities.

Patients and methods: Included were 79 patients with 210 pathological nodes, who underwent primary irradiation or chemoradiation. Several nodal characteristics were assessed on the planning CT scan. In addition, the 3D-dose distribution in the nodes was calculated by the planning system to allow for evaluation of underdosage in the pathological nodes and to correlate these results with control in the neck. Analysis was done on patient level (regional control) and node level (nodal control).

Results: For regional control, total nodal volume and the use of chemotherapy in addition to radiation were significant prognostic factors. For nodal control, also the presence of central necrosis and radiological extranodal spread were of importance. In case of radiotherapy alone, a minimal dose < 95% of the prescribed dose was associated with worse control. In case of combined modality treatment, the minimal radiation dose was of less importance.

Conclusions: Nodal volume and chemotherapy are the most important prognostic factors to control pathological nodes in the neck. Radiological central necrosis and extranodal growth, nodal volume and chemotherapy were significant prognostic factors for nodal control. Additionally, it appears that regional control in patients treated with primary radiation alone or with chemoradiation in case of a total nodal volume of more than 3.0 cm results in an unacceptable high risk on regional recurrence.

Introduction

The status of the neck nodes is a major determinant of outcome in patients with squamous cell head and neck cancer (SCHNC). Patients with cervical neck node metastases show worse disease specific survival (DSS) and develop more regional recurrences compared to patients without neck node metastases. In case of regional recurrence after primary radiation, salvage surgery is often possible, but is associated with additional morbidity and worse prognosis (7). In some institutions (9), it is general policy in patients with advanced nodal stages to perform a planned neck dissection after primary treatment with radiotherapy or chemoradiation. Residual pathological lymph node metastases in planned neck dissections are found in approximately 30% of these patients (9). Therefore, identification of patients with regional metastases who are at risk for regional failure after curative non-surgical treatment could possibly reduce the number of patients undergoing unnecessary surgical procedures.

The role of several prognostic factors for regional recurrence after primary radiation has been investigated. Previous studies showed that nodal size, radiological signs of extranodal spread and central necrosis are prognostic factors for regional control (1,10,13). However, in most of these studies, nodal diameters were assessed by clinical examination and not by more accurate methods including computed tomography (CT) and/or magnetic resonance imaging (MRI). Furthermore, the assessment of extranodal spread was mostly based on histological specimens and not on pre-operative radiological imaging techniques.

Therefore, the purpose of the present study was to evaluate the prognostic significance of a number of CT-based pre-treatment nodal and treatment-related characteristics with regard to regional control.

Material and methods

Patient characteristics

The population of this retrospective study consisted of a consecutive series of 79 patients who underwent primary radiotherapy or chemo-radiotherapy in the period from April 1999 to December 2002 for squamous cell carcinoma of the oral cavity (excluding the lip), nasal vestibule, oropharynx, hypopharynx and larynx. All patients had clinically positive neck nodes at diagnosis. The majority of patients (66%) were male. The median age was 62 years (range from 45 to 96 years). Histological diagnosis was confirmed by biopsy from the primary tumor in all cases. Patients with distant metastases were not included. T- and N-classification were assigned according to the staging system of the UICC 1997 (15). The pre-treatment characteristics are listed in Table 1.

Table 1: Tumour and nodal characteristics

Variable	Number	%
Tumour characteristcs (n=79)		
Primary tumor		
Oral cavity	10	13%
Oropharynx	25	32%
Hypopharynx	20	25%
Larynx	22	28%
Other (nasal vestibule)	2	3%
T-classification		
T1	3	4%
T2	19	24%
T3	26	33%
T4	31	39%
N-classification		
N1	22	28%
N2a	1	1%
N2b	24	30%
N2c	26	33%
N3	6	8%
Grade of differentation		
Well and moderately differentiated	41	52%
Poorly differentiated	25	32%
Unknown	13	16%
Individual nodal characterstics (n=210)		
Central necrosis		
No	116	55%
Yes	94	45%
Extranodal spread		
No	155	74%
Yes	55	26%
Nodal volume		
< 1.8 ml (diameter < 1.5 cm)	98	47%
1.9 - 14.0 ml (diameter 1.5 - 3.0 cm)	90	43%
> 14.0 ml (diameter > 3.0 cm)	22	10%
Conglomerate		
No	173	82%
Yes	37	18%

Radiotherapy

Patients were immobilized in supine position by the use of individually designed facial masks for reproducible positioning. A 3-mm slice, contrast-enhanced CT-scan was used for CT-planning.

The initial clinical target volume (CTV) consisted of the primary tumor, the pathological lymph nodes plus a 1 cm margin, and the elective nodal areas on both sides of the neck. For the planning target volume (PTV) a margin of 0.5 cm was applied, which was irradiated using 2 opposing lateral fields for the upper neck nodes and the primary site with an anterior field for the low jugular and supraclavicular lymph node areas. A posterior field was added in case no 95% coverage of the PTV could be achieved with an anterior field alone. If necessary, electron beams were used to boost the posterior cervical region. The dose of the electrons was specified at the 100%-isodose.

At our department, the general policy was to produce a treatment plan according to the ICRU guidelines, with coverage of the PTV of at least 95% of the prescribed dose. However, lower doses at areas just below the skin were generally accepted and in some cases a lower dose in some parts of the PTV was accepted as well, e.g. in case the total dose to the spinal cord was unacceptable or in the vicinity of field junctions. To get an impression of the actual total dose in the pathological lymph nodes, 3D-dose distributions and dose volume histograms were recalculated for each individual pathological node. The minimum doses were calculated as well as the volume percentage of each node receiving more than 67 Gy (V67).

Forty-two patients (53%) received accelerated radiotherapy alone and 37 patients (47%) were treated with radiotherapy and chemotherapy. Radiotherapy was delivered using megavoltage equipment (6 MV linear accelerator). The initial PTV was irradiated with 23 fractions of 2 Gy (5 times a week/once a day). Additionally, the primary tumor and pathological lymph nodes were boosted up to a total dose of 70 Gy. In case of primary radiotherapy alone, accelerated radiotherapy with a concomitant boost technique was used with a sixth fraction on Fridays from the second to the sixth week with an interval of at least 6 hours. In these cases, the overall treatment time was 6 weeks. In case of chemoradiation, conventional fractionation using 5 fractions per week was used. Some patients were treated with alternating chemoradiation and in these patients the total dose was 60 Gy. In the remaining patients, the total dose was 70 Gy.

Chemotherapy

Chemotherapy was given in 37 patients (47%). Twelve patients received induction chemotherapy (4 courses of cisplatinum 100 mg/m^2 + 5-FU 1000 mg/m^2 by continuous infusion every 3 weeks), 16 patients concomitant chemoradiation (3 courses of cisplatinum 100 mg/m^2 in week 1, 4 and 7) and 9 patients received alternating chemoradiation (4 courses of cisplatinum 100 mg/m^2 + 5-FU 1000 mg/m^2 by continuous infusion in week 1, 4, 7 and 10, with radiotherapy in week 3 and 4, 5 and 6, and 8 and 9 to a total dose of 60 Gy). All patients with unresectable disease were treated with concomitant chemotherapy. Induction chemotherapy or alternating chemoradiation was only administered in patients that participated in a randomised study.

Statistics

Data were analyzed in two different ways. First, the prognostic significance of the nodal characteristics was analyzed based on individual patient characteristics, referred to as regional control (N=79). A regional recurrence was defined as a persistent node after radiotherapy or chemoradiation as assessed at a minimum of 6 weeks after completion of treatment or a new pathological node after an initial complete response. Patients were followed every 2 months in the first year after treatment, every 3 months in the second year, and every 6 months thereafter. Generally, follow-up consisted of clinical examination of the neck while additional investigations were done in case of suspicious findings.

Second, we performed an analysis based on characteristics per node (N= 210), which is referred to as nodal control. Regional and nodal control was estimated from the first day of radiotherapy. In the univariate analysis, curves for regional and nodal control were estimated with the Kaplan-Meier method and compared by using the log rank test. A multivariate analysis was performed using the Cox proportional hazards model.

Results

Assessment of lymph node characteristics

The clinical lymph node status was assessed using the planning-CT scan in all cases. Neck nodes were considered pathological in case of the presence of central necrosis on CT and/or positive cytology and in case of a minimal axial diameter on CT of more than 10 mm, and more than 11 mm in level II (16,18,19). In the 79 patients included in the study, a total number of 210 pathological cervical nodes were identified. All 210 pathological lymph nodes were delineated on the pre-treatment planning CT-images. Location of the nodes to specific lymph node levels was assessed according to the consensus recommendations for delineation of node levels presented by Gregoire in 2003 (6,12). Patients, in which the pathological nodes could not be differentiated from the primary tumour, were excluded from the analysis. The interval between the planning-CT scan and the start of treatment varied from 7 to 14 days. Central necrosis was scored positively for lymph nodes with a hypo-dense centre or an inhomogeneous aspect (4,10). If nodal borders could not be clearly differentiated from the surrounding tissues, lymph nodes were classified as having extranodal spread (17). Lymph nodes in groups close together were scored as multiple node conglomerates. Nodal volumes were calculated by the planning system and were divided into 3 groups, including 0.1–1.8 ml, 1.9–14.0 ml and > 14.0 ml. Assuming sphere-shaped nodes, the corresponding tumour diameters are ″ 1.5 cm, 1.6-3.0 cm and > 3.0 cm, respectively. The lymph node characteristics are listed in Table 1.

Patient-based analysis (N = 79)

Regional and nodal control were based on clinical examination. Radiological imaging and/or ultrasound of the neck with fine needle aspiration were only performed when indicated. The regional control rate in all patients at 2 years was 65%. In the univariate analysis, regional control was significantly associated with central necrosis (p=0.03) and total nodal volume (p=0.005). Treatment modality showed a trend towards improved regional control (p=0.07) in case of chemoradiation. Number of lymph nodes, extranodal spread and histological grade showed no significant relation with regional control (Table 2). The standard policy in case of persistent neck nodes after completion of treatment or regional recurrences was salvage neck dissection. Curative salvage neck dissection was not performed in case of distant metastases, inoperable local recurrence, medical reasons and/or patient refusal.

Table 2: Results of the univariate analysis with regard to regional control and nodal control

Variable	Patient characteristics (regional control)			Nodal characteristics (nodal control)		
	Number	2-year regional control	Log Rank	Number	2-year nodal control	Log Rank
Central necrosis			p=0.03			p<0.001
No	28	78%		116	95%	
Yes	51	58%		94	72%	
Total tumor volume			p=0.005			p<0.001
< 1.8 cc	54	71%		98	96%	
0 - 14 cc				90	81%	
> 14 cc	25	52%		22	58%	
Chemotherapy			p=0.07			p=0.01
radiotherapy	42	50%		100	78%	
chemoradiation	37	83%		110	95%	
Number of lymph nodes			ns			ns
1 node	24	57%		24	57%	
2 nodes	22	78%		22	78%	
> 2 nodes	33	64%		33	64%	
Extranodal spread			ns			p=<0.001
No	43	71%		155	93%	
Yes	36	55%		55	57%	
Histological grade			ns			ns
well or moderately differentiated	41	57%		151	81%	
poorly differentiated	25	66%		51	87%	
Chemotherapy regimen						ns
induction				24	92%	
concomitant				86	96%	
Minimal dose						p=0.04
< 67 Gy				105	77%	
> 67 Gy				105	93%	

ns = not significant

An additional analysis stratified by chemotherapy was performed. Among patients treated with chemotherapy and radiotherapy, regional control was excellent in the group with total nodal volumes smaller than 14 cc (91% at 2 years), but decreased to 64% in the group with larger total nodal volume (p=0.021). The group treated with radiotherapy alone showed a similar effect (p=0.001), although the regional control rate at 2 years in the group with smaller total nodal volumes was worse compared to that found in the chemoradiotherapy group (p=0.02), 57% and 96%, respectively (Table 3).

Table 3: Results of the multivariate analysis with regard to regional and nodal control

Variable	Score	Regression coefficient (b)	SE (b)	P-value	RR	95%-ci
Regional control						
Total nodal volume	0.1 - 14.0 cc vs. > 14.0 cc	1.28	0.46	0.006	3.58	(1.45 - 8.83)
Chemotherapy	radiotherapy vs. chemoradiation	0.91	0.46	0.05	0.40	(0.16 - 0.99)
Nodal control						
Central necrosis	no vs. yes	1.47	0.65	0.03	4.34	(1.21 - 15.64)
Extranodal spread	no vs. yes	1.10	0.48	0.02	3.01	(1.19 - 7.65)
Nodal volume				< 0.001		
1.9 - 14.0 cc	compared to < 1.8 cc	1.21	0.67	0.07	3.36	(0.91 - 12.38)
> 14.0 cc	compared to < 1.8 cc	2.70	0.72	< 0.001	14.91	(3.67 - 60.55)
Chemotherapy	radiotherapy vs. chemoradiation	1.09	0.52	0.03	0.33	(0.12 - 0.92)

In the multivariate analysis, total nodal volume and chemotherapy were significantly associated with regional control. No such association was found for the other variables (Table 4).

Node-based analysis (N = 210)

At 2 years, nodal control was achieved in 85% of pathological neck nodes. In the univariate analysis, significant associations with nodal control were found for nodal volume (p<0.001), central necrosis (p<0.001), extranodal spread (p<0.001), chemotherapy (p=0.01) and minimal dose (p=0.04)(Table 2). No significant association was found between grade of differentiation and nodal control.

Again, an additional analysis was performed stratified by chemotherapy. Among patients treated with radiotherapy alone, the 2-years nodal control rate gradually decreased with larger volumes. However, among those treated with radiotherapy and chemotherapy, nodal control was excellent in case of nodal metastases ” 3.0 cm, but significantly deteriorated in case of nodes > 3.0 cm. In the subset of patients with a nodal diameter 1.6-3.0 cm, a significant difference was noted between those treated with radiotherapy alone and those treated with radiotherapy and chemotherapy (p=0.002), while no such differences were found for smaller or larger nodes (Table 3). Central necrosis was a significant prognostic factor among patients treated with radiotherapy alone as well as among those treated with radiotherapy and chemotherapy, with a trend towards better nodal control in case of combined modality treatment. Among patients treated with radiotherapy alone, a significant difference was noted between the nodes that received at least 95% of the prescribed dose and the nodes that received less than 95% of the prescribed dose (p=0.009)(Table 3). No such difference was found in case patients were treated with radiotherapy and chemotherapy. In the multivariate analysis, central necrosis, extranodal spread, nodal volume and chemotherapy were significantly associated with nodal control (Table 4).

Table 4: Results of the analysis with regard to regional and nodal control stratified by chemotherapy

Variable	Score	2-years locoregional control	
		Radiotherapy alone	Chemoradiation
Regional control according to total nodal volume			
0.1 - 14.0 cc		96%	91%
> 14.0 cc		57%	64%
P-value		p = 0.001	p = 0.021
Nodal control according to total nodal volume			
0.1 - 1.8 cc		94%	100%
1.9 - 14.0 cc		63%	98%
> 14.0 cc		56%	60%
P-value		p < 0.001	p < 0.001
Nodal control according to minimal dose per node			
Minimal dose 0-67 Gy		90%	100%
Minimal dose > 67 Gy		61%	92%
P-value		p=0.009	p = 0.066

Discussion

The negative prognostic effect of pathologic neck nodes in head and neck cancer is widely accepted, though the prognostic values of specific nodal characteristics are less clear. The results of the present study showed that regional control is significantly associated with total nodal volume and appeared to be better with adding chemotherapy to radiation. Additionally, nodal control was significantly worse in case of larger nodal volumes, no chemotherapy, the presence of radiological central necrosis and the presence of radiological extranodal spread.

Several others reported on regional control after primary radiotherapy (1, 7). In these studies, isolated nodal failures were found in 6 to 18 % of the cases, which seems to be better as the results found in the present study. A number of explanations for these apparent differences can be presented. First, in our study all regional failures were taken into account independent from the response of the primary tumour, while some of the aforementioned studies only included isolated nodal failures, when the primary tumour was still in complete remission. Second, in most other studies, nodal size was assessed by clinical examination while in our study nodal size was assessed on plannings-CT. It cannot be excluded that the size of the nodal diameter is overestimated at clinical examination, which is in accordance with our experience during the analysis of the present study. Without any doubt, assessment of nodal volume using CT-data is more accurate than by clinical examination. Third, in some studies, not only patients with pathological lymph node metastases < 3.0 cm were included, but also patients with N0 necks, while in our study, only patients staged N+ were included which negatively biased the results (7).

The association between total nodal volume and regional control was also studied by Hermans et al. (7), who found deteriorating regional control with increasing total nodal volumes, particularly when the nodal volume was > 14.5 ml, which is in accordance with the findings of the present study. We also found a striking deterioration of regional and nodal control in case the total nodal volume was > 14.0 ml. It is clear that primary radiation alone or chemoradiation in case of a total nodal volume of more than 3.0 cm is not sufficient. In the present study, nodal control was significantly associated with radiological central necrosis. However, the difference in regional control between patients with and without radiological central necrosis was not statistically significant, which could be due to the relatively limited number of patients included in this study. Previous studies showed that the presence of central hypodense zones on CT correlated well with a high incidence of nodal necrosis (14). These hypodense necrotic zones on contrast image CT-scans identify areas of hypo-angioperfusion, and could harbour hypoxic cells, which could explain the negative impact on regional and nodal control as hypoxic cells are less radio- and chemosensitive (10). Although less striking, in the analysis for nodal control, central necrosis was of importance among patients treated with radiotherapy alone as well as those treated with chemoradiation.

Several studies showed that extranodal spread is one of the most important prognostic factors in patients with cervical metastases regarding regional recurrence (8, 20). In all these studies, extranodal spread was based on histological specimen. In the present study, radiological extranodal spread was significantly associated with nodal control. However, no significant relation was found between extranodal spread and regional control, which could be due to the relatively small number of patients. Several authors investigated the role of CT for the detection of extranodal spread (2, 20, 21). In these studies, a sensitivity up to 100% was found, however the specificity in these studies varied from 60% to 78%. The fact that we did not find a significant correlation between radiological extranodal spread and regional control could therefore also be explained by the inaccuracy of CT with regard to the detection of extranodal spread. Minimal received nodal dose was no independent significant predictor of nodal control. Previous studies (1) were also not able to show a dose-effect relationship on regional recurrence. Although, underdosage was of no significant importance in the multivariate analysis for nodal control, the results of the stratified analysis suggested that a minimal nodal dose less than 95% of the prescribed dose had a stronger effect on nodal control in nodes treated with radiotherapy alone as compared to nodes treated with chemotherapy and radiotherapy. Apparently, the negative prognostic effect of this suboptimal dose is diminished by the additional effect of chemotherapy. In patients included in the present study, only conventional radiation techniques were used and in some cases a minimal dose less than 95% of the prescribed dose was accepted in situations in which there were no alternatives to further optimise the dose distribution in the PTV without compromising the probability on severe radiation-induced morbidity, in particular with regard to the spinal cord. These data show that patients treated with radiotherapy alone are more at risk for nodal failure in case of a suboptimal dose planning. Possibly, with the use of IMRT, these areas of the PTV receiving less than the desired dose could overcome this problem (11). The effect of dosimetric factors on regional recurrence in IMRT treated patients was investigated by Feng et al. (5). In this study, no significant relation was found between in-field recurrences (more than 95% of target volume received the prescribed dose), marginal recurrences and out-field recurrences (respectively 25 – 95% and less than 25% of target volume received prescribed dose).

Bussels et al. (3) investigated the effect of dosimetric factors on regional control in patients irradiated by mostly 3-D conformal, parotid sparing technique. This study showed that the majority of regional recurrences were in-field recurrences. A minority of regional recurrences occurred in areas of underdosage. However, this analysis was performed on a small population of only 14 patients, which possibly had impact on the power of the study.

In conclusion, total nodal volume and chemotherapy are significant prognostic factors for regional control. Radiological central necrosis and extranodal growth, nodal volume and chemotherapy were significant prognostic factors for nodal control. Additionally, it appears that regional control in patients treated with primary radiation alone or chemoradiation with a total nodal volume of more than 14 ml results in an unacceptable high risk of regional recurrence.

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