4

Distant metastases in head and neck carcinoma: Identification of prognostic groups with MR imaging

Redina Ljumanovic
Johannes A. Langendijk
Otto. S. Hoekstra
C. René Leemans
Jonas A. Castelijns

European Journal of Radiology
2006; 60:58-66

ABSTRACT

Purpose: To evaluate retrospectively the prognostic significance of lymph node parameters assessed on pretreatment magnetic resonance (MR) images for development of distant metastases in patients with head and neck squamous cell carcinomas.

Materials and methods: Pretreatment MR images of 311 patients were retrospective reviewed for the presence of lymph nodes at specific neck node levels as well as the size and the presence of a number of lymph node characteristics including extranodal spread, central necrosis and number and volume of ipsi- and contralateral nodes. Of these patients, 174 (56%) had MRI-positive nodes (defined as nodes with minimum axial diameter >8 and >4 mm for paratracheal level and retropharyngeal nodes).

Results: The 2-year distant-metastasis free survival rate (DMFSR) for patients without MRI-positive nodes was 94% compared to 75% for those patients with MRI-positive nodes. In patients with MRI-positive nodes, results of multivariate analysis with the Cox regression model yielded statistical significance for presence of extranodal spread (ENS), detected on MRI, as the only independent prognostic factor associated with the 2-year DMFSR ($p=0.002$). Based on the analysis, three risk groups regarding the DMFSR could be identified. Low-risk group (DMFSR:94%) consisted of patients without MRI-positive nodes. Intermediate-risk group (DMFSR:81%) consisted of patients with MRI-positive nodes without ENS. High-risk group (DMFSR:59%) consisted of patients with MRI-positive nodes and ENS as shown on MRI ($p<0.0001$). Statistical separation for different tumor locations showed MRI-determined ENS (larynx: $p=0.05$; oropharynx: $p=0.04$; oral cavity: $p<0.001$), lowjugular/posterior triangle nodes (oropharynx: $p=0.02$), paratracheal nodes (larynx: $p=0.03$), and contralateral node volume >5 cm^3 (larynx: $p=0.03$; oral cavity: $p=0.02$) to be significant predictors with regard to DMFSR.

Conclusion: Especially patients with on MRI demonstrating extranodal spread and with suspicious nodes at lowjugular/posterior triangle (oropharyngeal cancer) or paratracheal level (laryngeal cancer), or with contralateral enlarged nodes (laryngeal and oral cavity cancer) are at high risk for developing distant metastases and this subset of patients might benefit from supplementary imaging screening (CT-chest, PET-scan).

INTRODUCTION

In head and neck squamous cell carcinomas (HNSCC) the lymph node involvement is an important prognostic factor and has major implications for the choice of treatment and influences local-regional recurrence and development of distant metastases [1,2]. The prevalence of distant metastases in HNSCC at autopsy (37-57%) is much higher than in clinical studies (4-26%) [3-5]. Patients with distant metastases are generally not considered curable and often receive only palliative treatment.

Given the relatively low incidence of distant metastases at presentation, it is warranted to establish certain guidelines for establishing which patients should undergo evaluation for the presence of distant metastases. It is important to identify patients in whom more diagnostic tools (computed tomography-CT, positron emission tomography-PET, and magnetic resonance (MR) imaging) should be applied to detect distant metastases and to select patients who may theoretically benefit from novel adjuvant systematic therapy in the future.

Nodal metastases are detected with imaging modalities on the basis of size, presence of non-contrast enhancing parts within lymph nodes caused by tumor necrosis, and extranodal tumor spread. Size is the most often used criterion for suspicion. As the size of normal lymph nodes varies according to the level in the neck, and because small metastatic deposits inside lymph do not always cause enlargement of a lymph node, it is very difficult to define optimal size criteria [6]. Van den Brekel found that 102 out of 144 (71%) metastatic lymph nodes in the neck had a minimal axial diameter smaller than 1 cm [6]. In contrast, the detection of necrosis and extranodal spread in patients with a primary head and neck tumor is a reliable criterion for lymph node metastases; it is unfortunately quite rare or not visible in small positive lymph nodes [7-10].

Until now, several studies have focused on the correlation between clinical or histopathologic staging of cervical node metastases and the development of distant metastases of HNSCC. A number of authors reported on risk factors significantly associated with development of distant metastases, such as a clinically palpable neck mass, multiple lymph nodes, large lymph node metastases, bilateral and lowjugular lymph node metastases, extranodal spread as assessed by histological examination, locoregional tumor recurrence and second primary malignancies [1,3,11,12]. As reviewed by Spector et al. [13] the highest incidence of distant metastases occurred more in hypopharyngeal than laryngeal carcinoma and was significantly related to more advanced initial tumor presentation.

However, to our knowledge no data are available with regard to the prognostic significance of MR imaging determined lymph node parameters in patients with HNSCC and their correlation with the development of distant metastases. This may be of vital importance since many patients currently undergo non-surgical treatment.

The main purpose of this study was first to evaluate the pretreatment MR imaging-determined parameters in the neck, as one of the prognostic factors for the development of distant metastases in patients with HNSCC, and second to identify possible high-risk groups of patients in the population as a whole and for different primary tumor locations who may benefit from an additional screening for distant metastases.

MATERIALS AND METHODS

Patient population

Patients included in this retrospective study were those who had pathologically proven head and neck squamous cell carcinoma or lymph node metastases from an unknown SCC and who had undergone pretreatment MR imaging that enabled adequate image interpretation. Patients with a previously treated carcinoma of head and neck or known distant metastases at the time of presentation were not included. Patients were treated between January 1994 and December 1999. Our local ethics committee does not require its approval or informed consent for retrospective review of patients' records and images.

Three hundred eleven patients with a median age of 62 years, ranging from 32 to 87 years, fulfilled these criteria. There were 239 male patients (77%; mean age, 62 years; median, 62 years) and 72 female patients (23%; mean age, 61 years; median, 59 years). Tumors were located in the oral cavity in 12% (n=39), in the oropharynx 33% (n=103), in the larynx 51% (n=158), or in the hypopharynx 2% (n=6). In 2% of the cases (n=5), the patients had a lymph node squamous cell carcinoma from an unknown primary. The stage of disease was determined clinically according to the recommendations of the Union Internationale Contre le Cancer 1997 [14]. Tumor and treatment characteristics in the 311 patients are listed in Table 1.

MR imaging

MR images were obtained with 1.0-T or 1.5-T MR system (Impact/Vision; Siemens Medical Solutions, Erlangen, Germany). MR imaging studies were performed by using an anterior surface neck coil. A multisection, two-dimensional Fourier-transform spin-echo pulse sequence was used in all patients. In all patients, the imaging protocol included axial T1-weighted spin-echo MR imaging (repetition time msec/echo time msec, 300-780/15; section thickness, 3, 4 or 5 mm with 1-mm intersection gap), axial intermediate-weighted (2200-4200/16-22) and

Table 1: Tumor and treatment characteristics

Variable	Number	% Of 311
T – classification		
T0	5	2
T1	53	17
T2	106	34
T3	94	30
T4	53	17
N – classification[a]		
N0	197	63
N1	46	15
N2	57	18
N3	11	4
Treatment of primary tumor		
Surgery	17	5
Radiotherapy	153	49
Surgery and Radiotherapy	120	39
Radiochemotherapy	18	6
Refused treatment	3	1
Treatment of neck		
Surgery	16	5
Radiotherapy	125	40
Surgery and Radiotherapy	112	36
Radiochemotherapy	17	6
No treatment	38	12
Refused treatment	3	1

T0: unknown primary tumor. [a] N-classification based on physical examination without knowledge of data obtained with US and/or MR imaging.

axial T2-weighted (2200-4200/90-98) fast spin-echo MR imaging and contrast material-enhanced axial T1-weighted spin-echo imaging (300-780/15; section thickness, 3, 4 or 5 mm with 1-mm intersection gap) after a bolus injection of 0.1 mmol/kg of bodyweight Gd-DTPA (Magnevist; Berlex, Wayne, NJ). Contrast-enhanced T1-weighted MR imaging with fat suppression (470-730/15) was performed in 68 patients. The field of view was kept as small as possible (200 x 200 mm). Acquisition times varied from 3 to 6 minutes.

Follow-up

Patients were followed up at regular intervals by the clinicians, i.e., every 2 months in the first 2 years after completion of the treatment and every 4-6 months thereafter. As basis for data acquisition and analysis, we have defined the distant metastases as tumor spread to other organ systems: (1) nonlymphatic metastases to other organs, the most common being pulmonary parenchymal metastases (skin, bone, etc.) or (2) lymph node metastases to other than regional lymph nodes (abdominal, etc.). Routine radiographs of the chest were made yearly, supplemented by a CT scan of the thorax if suspicious was raised on the radiograph. Special investigations, such as bronchoscopy with sputum cytology, bone scanning, serum liver function tests, abdominal ultrasound scanning, and brain scans, were performed when indicated. The minimum follow-up period was 2 years. The mean follow-up time (for this review with treatment failure at distant sites or with last patient contact) was 2.9 years (range, 7-85 months).

Evaluation of MRI-positive lymph nodes

The mean delay time between the MR study and the start of primary therapy was 24 days (median, 21 days). All pretreatment MR images were retrospectively reviewed and evaluated by 2 examiners in consensus, who were blinded to results of other clinical examinations, surgicopathological findings or clinical outcome. The lymph nodes were divided in six levels according to the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) [15], as follows: I submental and submandibular, II subdigastric, III midjugular, IV lowjugular, V posterior triangle and supra/infraclavicular level, and VI paratracheal level. Additionally, we evaluated the presence of retro(pharyngeal) lymph nodes and these formed a separate group.

We compared pretreatment MR imaging determined lymph node parameters and development of distant metastases. MRI-positive nodes were lymph nodes at levels I–V equal to or greater than 8 mm in minimum axial dimension; nodes less than 8 mm were considered as MRI-negative nodes and were not measured. The nodes located at paratracheal level and retropharyngeal nodes equally to or greater than 4 mm in smallest dimension were considered as MRI-positive lymph nodes. Lymph node clusters at same level were considered to be one lymph node.

A criterion for declaring extranodal spread (ENS) was a MRI-positive lymph node, with capsular contour irregularity and/or infiltration of adjacent planes. The presence of non-contrast-enhancing parts inside MRI-positive lymph node or irregular contrast enhancement was a criterion for declaring nodal necrosis.

The lymph node outlines were traced manually on T1-weighted MR images, with use of a computerized image analysis tool that is available as part of our hospital's picture archiving and communication system (Centricity Radiology RA 600, version 6.1; GE Medical Systems). The volume of the lymph node was calculated in cubic centimeters by multiplying the value of the lymph node area in each section in which the lymph node was present by the sum of the section thickness and intersection gap and then summing the resultant values.

Stratified into categories, lymph node volume was compared to the presence of extranodal spread.

Statistical analyses

The distant-metastasis free interval was defined as the date of pretreatment MR imaging to the date of the first sign of distant metastases and was estimated with the Kaplan-Meier method. The log-rank test was used to test the statistical significance of differences between curves. Univariate and multivariate analyses using the Cox proportional hazards model were performed to identify determinants associated with the DMFSR (distant-metastasis free survival rate). Differences in the mean values between groups were tested with Student's t-test or non-parametric tests where appropriate.

As the different MRI detected lymph node characteristics can only be assessed in the patients with MRI-positive lymph nodes (=MRI-LN positive group), the groups of patients without and with MRI-positive nodes (MRI LN-negative and positive groups) were analyzed separately in the statistical analyses. The DMFSR of patients in these groups was evaluated. In the subset of MRI-LN negative patients, the following variables were entered into the statistical model: patient sex (male versus female), age (0-62 versus >62 years), primary tumor location (oral cavity versus oropharynx versus larynx versus hypopharynx versus unknown primary) and T classification (T0 versus T1 versus T2 versus T3 versus T4).

In group of patients with MRI-positive lymph nodes the following variables were entered in the multivariate model: patient sex, age, tumor location, T classification and lymph node parameters ipsilaterally and/or contralaterally (absent versus present): total number of lymph nodes at levels I-II-III, total number of lymph nodes at levels IV-V, number of lymph nodes at level VI, number of retro(pharyngeal) lymph nodes, extranodal spread, nodal central necrosis and classified total lymph node volume, separately ipsilateral and contralateral ($<5\ cm^3$ versus $>5\ cm^3$). *P* of less than 0.05 was considered to indicate a statistically significant difference.

Prognostic model

The MR imaging factors that were identified as independent prognostic factors for DMFSR in the multivariate analysis were pooled in a prognostic model to assess a subset of patients with a possibly very poor outcome with regard to the DMFSR. Based on these risk factors, three prognostic groups were defined in the whole patient population. In addition, DMFSR of these three groups was estimated on the Cox proportional hazard model with correction for confounding factors. Moreover, to investigate whether the association between the independent outcome variables was modified by other variables (e.g., primary tumor site and primary treatment), interaction terms were included in the univariate and multivariate model as well. The statistical analyses were performed using the SPSS/PC software package (version 11.0; SPSS, Chicago, III).

RESULTS

MRI-positive lymph nodes

The pretreatment MRI-positive nodes were detected in 174 out of 311 patients (56%). The distribution of these lymph nodes in the different neck levels is presented in Table 2. The mean lymph node volume of the MRI-positive nodes was 11.35 cm^3 (median, 5 cm^3; range, 0.3-122 cm^3). A significant association was found between N classification and lymph node volume (analysis of variance, p<0.001) (Table 3). About 30 patients out of 174 patients (17%) had MRI-positive nodes bilaterally. The mean lymph node volume ipsilateral was 10.5 cm^3 (n=158; range, 0.3-120 cm^3) and contralateral was 4.1 cm^3 (n=76; range, 0.4-53.2 cm^3). Ipsilateral, extranodal spread (ENS) was observed on

Table 2. The number of cervical lymph nodes according to primary tumor location

Lymph nodes	Tumor locations					
	Hypopharynx	Oral cavity	Oropharynx	Larynx	Unknown primary	Total (%)
Ipsilateral						
Level I[a]		9	7			16 (7%)
Level II	3	23	66	51	4	147 (67%)
Level III	2	3	16	8		29 (13%)
Level IV			5	3		8 (4%)
Level V			2			2 (1%)
Level VI	1	1	1	6		9 (4%)
RP nodes			8	1		9 (4%)
Total	6	36	105	69	4	220
Contralateral						
Level I[a]		2	2			4 (4%)
Level II	1	9	25	26	1	62 (70%)
Level III		2	5	6		13 (15%)
Level IV			1	1		2 (2%)
Level V						
Level VI			3			3 (3%)
RP nodes			5			5 (6%)
Total	1	13	41	33	1	89

[a] I: submental and submandibular level; II: subdigastric level; III: midjugular level; IV: lowjugular level; V: posterior triangle and supra/infraclavicular level; VI: paratracheal level; RP: (retro)pharyngeal nodes.

Table 3: Mean lymph node volume according to N classification

N - category	Mean lymph node volume (cm^3)	No. of patients	95% CI
N0	4.7	73	(3.3 - 6.2)
N1	7.0	42	(4.9 - 9.0)
N2	14.8	49	(11.5 - 18.5)
N3	61.2	10	(31.9 – 90.5)
Total	11.35	174	(8.7 - 14.0)

Note. –P value for correlation of N category with lymph node volume was <0.001.

MR imaging in 44 out of 158 patients (28%) and in 97 patients central necrosis was observed (61%). Contralaterally, in 5 out of 76 patients (7%) lymph nodes exhibited ENS and in 36 patients central necrosis was present (47%). Of the recurrences, local treatment failure occurred in 76 (24%) of 311 patients and 18 patients (6%) developed a regional recurrence. A borderline significant association was found between locoregional control and distant metastases ($p=0.06$).

Distant-metastases free survival rate (DMFSR)

Fifty-four patients (17%) out of 311 developed the distant metastases. Distant metastases were observed in the lung in 36 out of these 54 cases (67%), bone in 8 cases (15%), skin in 5 cases (9%), liver in 3 cases (5%), and brain in 2 cases (4%). The DMFSR among patients with different primary sites differed significantly. The 2-year DMFSR among patients with laryngeal cancer was 91% as compared to 80% among those with an unknown primary, 77% among patients with oropharyngeal cancer, 74% in oral cavity tumors, and 67% among patients with hypopharyngeal cancer ($p=0.01$).

In the univariate analysis, a statistically difference was observed between the MRI-LN negative and the MRI-LN positive group. The DMFSR at 2 years in the MRI-LN negative group was 94% as compared to 75% in the MRI-LN positive group ($p<0.0001$). In the univariate analysis, the total lymph node volume ipsilaterally and the presence of ENS on MRI (ipsi- and contralateral) were significantly associated with the DMFSR (Table 4).

In the multivariate analysis, ENS was the only independent predictor with regard to the DMFSR (hazard risk ratio (HR): 2.7; 95% CI: 2.1–7.0; $p=0.002$). No other independent prognostic factors were found. The representative cases of ENS as assessed on MR imaging are shown in Figs. 1-3.

Based on these results, 3 prognostic groups could be identified in the total patient population: (1) the low-risk group, i.e. 137 patients who were MRI-LN negative, (2) the intermediate-risk group, consisting of patients with MRI-positive nodes without ENS (128 patients), and (3) the high-risk group,

Table 4: Univariate analysis of MRI-LN positive group using Kaplan-Meier

Variable (174 patients, 44 events)	No. of patients	2-year DMFSR[a](%)	Survival Function[b]	df	Univariate P value
Sex			0.2	1	0.7
Male	135	77			
Female	39	70			
Age			0.2	1	0.6
0-62 years	106	77			
>62 years	68	73			
Tumor location			5.1	3	0.2
Oral cavity	28	63			
Oropharynx	75	74			
Larynx	60	81			
Hypopharynx	6	79			
Unknown	5	80			
T classification			3.1	4	0.5
T0	5	80			
T1	18	83			
T2	49	81			
T3	70	68			
T4	32	76			
Lymph nodes at levels I-II-III[c]			0.4	1	0.8
Not present	7	64			
Present	167	75			
Lymph nodes at levels IV-V			3.1	1	0.07
Not present	164	76			
Present	10	58			
Lymph nodes at level VI			0.3	1	0.5
Not present	165	76			
Present	9	62			
Retropharyngeal nodes			1.5	1	0.2
Not present	160	77			
Present	14	60			
Central nodal necrosis			2.8	1	0.09
Not present	65	83			
Present	109	70			
Extranodal spread			10.6	1	0.001
Not present	128	81			
Present	46	59			
Total lymph node volume ipsilateral			10.9	1	0.001
Not present	16	88			
Present	158	74			
Total lymph node volume contralateral			0.0	1	0.9
Not present	98	72			
Present	76	74			

[a] Numbers are percentages.
[b] Calculated with the long-rank test.
[c] I: submental and submandibular level; II: subdigastric level; III: midjugular level; IV: lowjugular level; V: posterior triangle level; VI: paratracheal level.

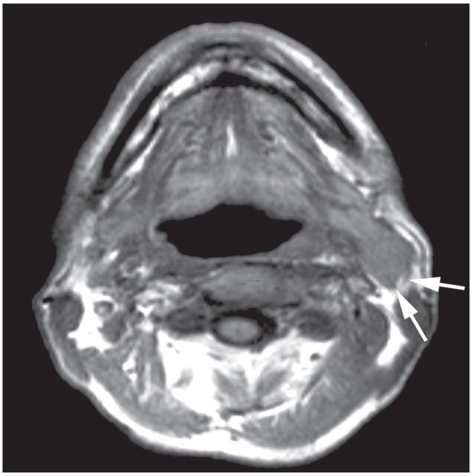

Figure 1: A 57 year-old patient with a T2N2a supraglottic laryngeal carcinoma treated with curative radiotherapy. Axial T1-weighted spin-echo (600/15) MR image depicting a lymph node with an irregular border (arrows) in the left subdigastric area, suspicious for extranodal spread of this node.

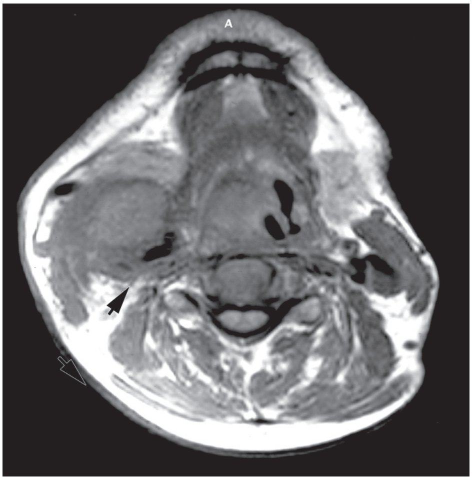

Figure 2: A 63 year-old patient with a T3N2b oropharyngeal carcinoma treated with chemoradiotherapy. Axial T1-weighted spin-echo (700/15) MR image shows a node with capsular contour irregularity and infiltration of adjacent planes, suspicious extranodal spread (arrows) in the right subdigastric area.

consisting of patients with MRI-positive nodes with ENS (46 patients). Ten patients out of the low-risk group (7%), 25 out of the intermediate-risk group (19%) and 19 patients out of the high-risk group (41%) developed distant metastases. The 2-year DMFSR estimated according to Kaplan-Meier, in the high-risk group was only 59% that was significantly worse compared to the intermediate-risk ($p=0.001$) and low-risk group ($p<0.0001$) where the DMFSR was 81% and 94%, respectively (Fig. 4).

Larynx

One hundred fifty-eight patients out of 311 patients (51%) had the laryngeal primary tumor. There were 131 male (83%) and 27 female (17%). Four patients were treated with surgery (2%), 28 patients (18%) with surgery combined with radiotherapy, 123 patients (78%) with irradiation alone, two patients (1%) with (chemo)radiation therapy, and one patient (1%) refused any kind of treatment. Fourteen patients (9%) underwent chemotherapy after the primary treatment. The 2-year DMFSR estimated according to Kaplan-Meier, in patients treated with surgery combined with RT was 70% that was significantly lower compared to patients treated with surgery (DMFSR:100%), with (chemo)radiation therapy (DMFSR:100%), and patients treated with irradiation alone (DMFSR:93%) ($p=0.01$). Seventeen patients (11%) developed the distant metastases.

Figure 3: A 50 year-old patient with a T3N2b oropharyngeal carcinoma treated with surgery combined with radiotherapy.

A Axial pre-gadolinium T1-weighted MR image obtained with a spin-echo pulse sequence (600/15) shows a lymph node with intermediate signal intensity at right side of subdigastric level with suspected extranodal spread (arrows) and central necrosis. A borderline node on left side at same level is depicted as well.

B Axial T2-weighted fast spin-echo (3000/98) MR image at corresponding level illustrates the lymph node with high signal intensity compared to axial T1-weighted MR image, suggestive of cystic degeneration or necrosis and obviously an irregular border. The lymph node on the left is shown with irregular signal intensity as well.

C Axial post-gadolinium T1-weighted spin-echo (600/15) MR image at corresponding level illustrates the lymph node with an irregular border. Within the node, there is tumor with widespread necrosis in the area corresponding to the low signal intensity area seen on the axial T1-weighted MR image. The lymph node on the left shows some irregularity in contrast enhancement as well and was proven to be tumor positive by US-guided FNAC.

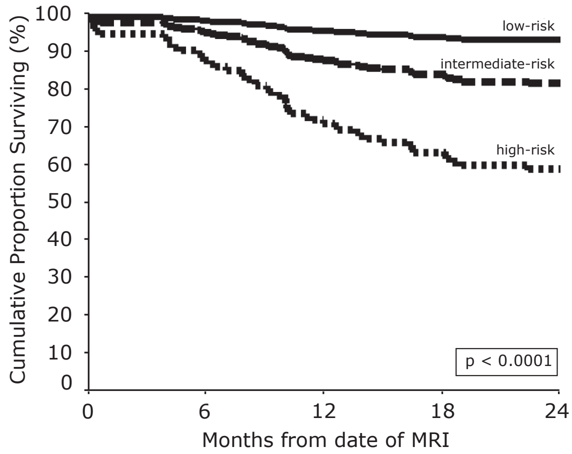

Figure 4: Estimated curves for distant metastasis free survival rate according to risk group.

Results of the multivariate analysis were as follows: total number of lymph nodes at level VI (HR: 5.3; 95% CI: 1.1–25.4; p=0.03), contralateral lymph node volume > 5 cm^3 (HR: 4.9; 95% CI: 1.2–20.5; p=0.03) and ENS (HR: 3.5; 95% CI: 1.0–12.5; p=0.05) were found to be independent significant prognostic risk factors with regard to DMFSR.

Oropharynx

About 103 out of 311 patients (33%) had the oropharyngeal primary tumor. There were 77 male (75%) and 26 female (25%). Nine patients were treated with surgery (9%), 61 patients (59%) with surgery combined with radiotherapy, 21 patients (20%) with irradiation alone, 11 patients (11%) with (chemo)radiation therapy, and 1 patient (1%) refused any kind of treatment. Ten patients (10%) underwent chemotherapy after the primary treatment. The 2-year DMFSR estimated according Kaplan-Meier was not significantly different between the distinctive treatments of the primary tumor (surgery, 89%; surgery combined with RT, 77%; RT, 76%; (chemo)radiation therapy, 73%; p=0.6). Twenty-three patients (22%) developed the distant metastases.
Results of the multivariate analysis yielded the significance of the following lymph node parameters: total number of lymph nodes at level IV-V (HR: 4.3; 95% CI: 1.2–14.9; p=0.02) and ENS (HR: 2.4; 95% CI: 1.0–5.8; p=0.04) were found to be independent significant prognostic risk factors in association with the DMFSR.

Oral cavity

Thirty-nine patients out of 311 patients (12%) had the primary tumor located in the oral cavity. There were 22 male (56%) and 17 female (44%). Three patients

were treated with surgery (8%), 28 patients (72%) with surgery combined with radiotherapy, four patients (10%) with irradiation alone and four patients (10%) with (chemo)radiation therapy. Six patients (15%) underwent chemotherapy after the primary treatment. According Kaplan-Meier, two-years DMFSR was not significantly different between the distinctive treatments of the primary tumor (surgery, 67%; surgery combined with RT, 71%; RT, 75%; (chemo)radiation therapy, 75%; p=0.9). Eleven patients (28%) developed distant metastases.
In the multivariate analysis, contralateral lymph node volume > 5 cm^3 (HR: 13.9; 95% CI: 1.4–138.4; p=0.02) and ENS (HR: 10; 95% CI: 2.8–36.1; p<0.001) were found to be independent significant prognosticators with regard to DMFSR.
Nodal necrosis was not found to be a significantly correlated with development of distant metastases both in the entire group and in the different subsites.

DISCUSSION

This retrospective study was performed on 311 patients with head and neck squamous cell carcinoma, in order to investigate the prognostic significance of pretreatment MR imaging of the lymph nodes of the neck for the development of distant metastases that may be readily accepted by clinicians, and be easily used for distant staging guidelines. Our results in the whole patient population yielded three distinctive prognostic groups (i.e., patients who were MRI-LN negative, patients with MRI-LN positive nodes without ENS and patients with positive nodes with ENS on MR imaging) with regard to the DMFSR, which enables the identification of a subset of patients at high risk for the development of distant metastases after initial treatment. In the high-risk groups, screening with supplementary techniques, including PET and CT-chest may be useful. Because most distant metastases arise in the lungs, CT-chest and PET-scan are probably the most optimal modalities to detect distant metastases [16]. Early detection may be of use in order to prevent local-regional treatment with considerable acute and late morbidity, such as concomitant chemoradiation and or extensive surgery with postoperative radiotherapy, particularly in case of extensive metastatic disease. In some cases, e.g. when only a solitary metastatic deposit is present, aggressive treatment of locoregional and metastatic disease may be an option and in some cases even curative. Also in these circumstances, early detection may be beneficial.
We will now discuss successively prognostic value of lymph node parameters at specific levels, the value of lymph node volume and the value of extranodal spread.
Leemans et al. [1] have stated that patients with three or more positive nodes were most at risk for having distant metastases. In this study, the number

of lymph nodes did not correlate significantly with the DMFSR. In a previous study of De Bree et al. [12], it was found that patients with four or more clinical lymph node metastases or lowjugular lymph node metastases had the highest incidence of distant metastases in head and neck carcinoma. In the present study, the analysis of the entire group showed a borderline significance of lymph nodes at levels IV (lowjugular) and V (posterior triangle). Subsequently, these lymph nodes were found to be significant predictive for the development of DMFSR in the subgroup of patients with oropharyngeal cancer. Detection of retropharyngeal nodes is beneficial in clinical practice, because metastases of these nodes are beyond the limits of neck dissection and suggest a very poor prognosis [17]. In the present study, in the entire group of patients with these nodes, no significant association was found with the DMFSR possibly due to limited number of patients with retropharyngeal nodes (5%). It is reported that paratracheal lymph node metastases carry a high risk for metastases to the mediastinum and distant sites [18]. The numbers of these lymph nodes in the entire group of study population was relatively low and not of statistical significance but well significant associated with the DMFSR in the patients with laryngeal carcinoma.
Until now, no other study has evaluated the MR imaging-determined volumetry of lymph nodes regarding any patient outcome in HNSCC. Hermans et al. [19] have suggested a significant correlation between CT-determined nodal tumor volume (especially enlarged lymph nodes metastases >14.5 mL) and the likelihood of regional failure after definitive radiation therapy in tonsillar carcinoma. In the present study, the current findings of the measurements of lymph node volumes in the univariate analysis showed an association with the DMFSR that disappeared in the multivariate analysis in the entire study population of MRI-LN positive patients. Statistical separation that was defined on the basis of different tumor localization yielded a strong significant association with the DMFSR of contralateral lymph node volume > 5cm^3 in oropharyngeal and in oral cavity carcinoma.
In previous studies, the presence of ENS as assessed by histological examination was also associated with an increased risk of distant metastases [1,3]. Others showed that ENS can be assessed with MR imaging, especially macroscopic extranodal spread [20]. Yousem et al. [9] have reported that the accuracy of MR imaging for detecting ENS with T1-weighted images in patients with suspect malignant cervical lymphadenopathy was high, namely 78%-90%. Although it was previously thought that ENS occurred only in large nodes, it is known that ENS can occur also in 23% of nonenlarged nodes [21]. In this study, ENS of lymph nodes as assessed on MR imaging was the most significant predictor of the development of distant metastases, both in the entire study population as well as in separate groups according different tumor sites. These findings

suggest that the presence of ENS is more important than other lymph node parameters.

As all patients were treated differently in our study population, the possibility whether the DMFSR may depend on the kind of loco-regional treatment was not significantly verified in our study. Layland et al. [22] reported no difference in survival between current approaches to treatment of the N0 neck in head and neck carcinoma. In univariate analyses of the present study, in which treatment was included as a variable, only patients with laryngeal cancer and treated with surgery combined with radiotherapy showed significantly association with very poor outcome. Patients treated with other modality did not prove to be relevant in these statistical analyses. However in our institution surgical treated patients are treated subsequently by radiation therapy, if histopathology shows extracapsular nodal spread. As a consequence this finding is clearly in accordance with our results, despite not performed histopathological correlations due to dissimilar number of lymph nodes determined with MR imaging or pathology. The association of different treatment modalities with the development of distant metastases may play a role, which should be investigated.

On the basis of our findings and the available literature, metastatic work-up in patients with low-risk disease, as we assessed a DMFSR of 94% at 2 years, may not be cost-effective and may therefore not be performed. In the high-risk group, in which the risk to develop distant metastases was 41%, patients should be screened routinely and comprehensively for the detection of distant metastases. Regarding the intermediate group, in which the risk to develop distant metastases was assessed in our study on 19%, further study should be performed regarding the yield of radiological screening (CT-thorax) on distant metastases. If this yield is high enough, this patient group or a part of this patient group should also be screened. If not extensive screening should be restricted to the high-risk group of patients, in which at least one lymph node with extranodal spread is found.

CONCLUSION

Especially patients with on MR imaging demonstrating extranodal spread and with suspicious nodes at lowjugular/posterior triangle (in patients with oropharyngeal cancer), or paratracheal level (in patients with laryngeal cancer), or with contralateral enlarged lymph nodes (in patients with laryngeal and oral cavity cancer) are at high risk for developing distant metastases and this subset of patients should undergo screening for distant metastases.

References

[1] Leemans CR, Tiwari R, Nauta JJ, van der Waal I, Snow GB. Regional lymph node involvement and its significance in the development of distant metastases in head and neck carcinoma. Cancer 1993; 71:452-6

[2] Leemans CR, Tiwari R, Nauta JJ, van der Waal I, Snow GB. Recurrence at the primary site in head and neck cancer and the significance of neck lymph node metastases as a prognostic factor. Cancer 1994; 73:187-90

[3] Alvi A, Johnson JT. Development of distant metastasis after treatment of advanced-stage head and neck cancer. Head Neck 1997; 19:500-5

[4] Leon X, Quer M, Orus C, del Prado Venegas M, Lopez M. Distant metastases in head and neck cancer patients who achieved loco-regional control. Head Neck 2000; 22:680-6

[5] Ferlito A, Shaha AR, Silver CE, Rinaldo A, Mondin V. Incidence and sites of distant metastases from head and neck cancer. ORL J Otorhinolaryngol Relat Spec 2001; 63:202-7

[6] Van den Brekel MW, Castelijns JA and Snow GB. The size of lymph nodes in the neck on sonograms as a radiologic criterion for metastasis: how reliable is it? AJNR Am J Neuroradiol 1998; 19:695-700

[7] Van den Brekel MW, Stel HV, Castelijns JA et al. Cervical lymph node metastasis: assessment of radiologic criteria. Radiology 1990; 177: 379-84

[8] Som PM. Detection of metastasis in cervical lymph nodes: CT and MR criteria and differential diagnosis. AJR Am J Roentgenol 1992; 158:961-9

[9] Yousem DM, Som PM, Hackney DB, Schwaibold F, Hendrix RA. Central nodal necrosis and extracapsular neoplastic spread in cervical lymph nodes: MR imaging versus CT. Radiology 1992; 182:753-9

[10] King AD, Tse GM, Ahuja AT, et al. Necrosis in metastatic neck nodes: diagnostic accuracy of CT, MR imaging, and US. Radiology 2004; 230:720-6

[11] Shingaki S, Suzuki I, Kobayashi T, Nakajima T. Predicting factors for distant metastases in head and neck carcinomas: an analysis of 103 patients with locoregional control. J Oral Maxillofac Surg 1996; 54:853-7

[12] De Bree R, Deurloo EE, Snow GB, Leemans CR. Screening for distant metastases in patients with head and neck cancer. Laryngoscope 2000; 110:397-401

[13] Spector JG, Sessions DG, Haughey BH, et al. Delayed regional metastases, distant metastases, and second primary malignancies in squamous cell carcinomas of the larynx and hypopharynx. Laryngoscope 2001; 111:1079-87

[14] Hermanek P, Hutter RVP, Sobin LH, Wagner G, Wittekind Ch, eds. TNM atlas: Illustrated guide to the TNM/pTNM classification of malignant tumours, 4th ed. Union Internationale Contre le Cancer and International Union against Cancer. 4th ed. Berlin, Heidelberg: Springer-Verlag; 1997. p. 5-49

[15] Robbins KT, Clayman G, Levine PA, et al. Neck dissection classification update: revisions proposed by the American Head and Neck Society and the American Academy of Otolaryngology-Head and Neck Surgery. Arch Otolaryngol Head Neck Surg 2002; 128:751-8

[16] Perlow A, Bui C, Shreve P, Sundgren PC, Teknos TN, Mukherji SK. High incidence of chest malignancy detected by FDG PET in patients suspected of recurrent squamous cell carcinoma of the upper aerodigestive tract. J Comput Assist Tomogr 2004; 28:704-9

[17] McLaughlin MP, Mendenhall WM, Mancuso AA, et al. Retropharyngeal adenopathy as a predictor of outcome in squamous cell carcinoma of the head and neck. Head Neck 1995; 17:190-8

[18] Amatsu M, Mohri M, Kinishi M. Significance of retropharyngeal node dissection at radical surgery for carcinoma of the hypopharynx and cervical esophagus. Laryngoscope 2001; 111:1099-103

[19] Hermans R, De Beeck KP, Van den Bogaert W, et al. The relation of CT-determined tumor parameters and local and regional outcome of tonsillar cancer after definitive radiation treatment. Int J Radiat Oncol Biol Phys 2001; 50:37-45

[20] King AD, Lei KI, Ahuja AT. MRI of neck nodes in non-Hodgkin’s lymphoma of the head and neck. Br J Radiol 2004; 77:111-5

[21] Som PM. Lymph nodes of the neck. Radiology 1987; 165:593-600

[22] Layland MK, Sessions DG, Lenox J. The influence of lymph node metastasis in the treatment of squamous cell carcinoma of the oral cavity, oropharynx, larynx, and hypopharynx: N0 versus N+. Laryngoscope 2005; 115:629-39