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## Morphological MRI criteria improve the detection of lymph node metastases in head and neck squamous cell carcinoma: multivariate logistic regression analysis of MRI features of cervical lymph nodes

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**Abstract** The aim was to evaluate whether morphological criteria in addition to the size criterion results in better diagnostic performance of MRI for the detection of cervical lymph node metastases in patients with head and neck squamous cell carcinoma (HNSCC). Two radiologists evaluated 44 consecutive patients in which lymph node characteristics were assessed with histopathological correlation as gold standard. Assessed criteria were the short axial diameter and morphological criteria such as

border irregularity and homogeneity of signal intensity on T2-weighted and contrast-enhanced T1-weighted images. Multivariate logistic regression analysis was performed: diagnostic odds ratios (DOR) with 95% confidence intervals (95% CI) and areas under the curve (AUCs) of receiver-operating characteristic (ROC) curves were determined. Border irregularity and heterogeneity of signal intensity on T<sub>2</sub>-weighted images showed significantly increased DORs. AUCs increased from 0.67 (95% CI: 0.61–0.73) using size only to 0.81 (95% CI: 0.75–0.87) using all four criteria for observer 1 and from 0.68 (95% CI: 0.62–0.74) to 0.96 (95% CI: 0.94–0.98) for observer 2 ( $p < 0.001$ ). This study demonstrated that the morphological criteria border irregularity and heterogeneity of signal intensity on T2-weighted images in addition to size significantly improved the detection of cervical lymph nodes metastases.

**Keywords** Head and neck · Lymph nodes · Metastases · MRI

### Introduction

The presence of cervical lymph node metastases is an important prognostic factor in patients with HNSCC as it worsens significantly the treatment outcome [1–8]. The

choice of management depends on the existence and extent of lymph node metastases in the neck. Therapy could consist of surgery, radiation therapy, chemotherapy, or a combined therapy. However, all these therapies have a considerable morbidity and mortality. Therefore, treatment

refinements like limitation of the field of radiation or a more selective neck dissection are necessary [9–15]. MRI is one of the imaging techniques that is used to guide treatment decisions, but the ability of MRI to discriminate between lymph nodes with and without metastasis is still poor [16].

A commonly used criterion for the assessment of cervical lymph node involvement on MRI is the short axial diameter, and several studies have been undertaken to determine the optimal cutoff size of the short axial diameter for discrimination between metastatic and non-metastatic lymph nodes. On MRI a commonly used size cutoff point is a short axial diameter of 10 mm, but a range varying from 9 to 15 mm has been described [17–21]. The challenge for radiologists remains the detection of metastases in small lymph nodes with a short axial diameter below 10 mm, because mere use of the size criterion will result in misclassification of these nodes as normal. In this respect, according to the literature, the performance of MRI is still poor for detection of lymph node metastases, and this concerns especially the detection of metastases in small lymph nodes [16].

In addition to the size criterion, the use of morphological criteria might have added value to detect metastatic disease in lymph nodes. The diagnostic value of morphological criteria has not been well evaluated in patients with HNSCC. In patients with rectal cancer, Kim et al. demonstrated that in addition to the size criterion, morphological criteria such as borders and heterogeneity could be helpful signs to predict nodal involvement [22].

The aim of our study was to evaluate the accuracy and additional diagnostic value of morphological criteria observed on MRI images, such as border irregularity and

heterogeneity of the signal intensity on T2-weighted images and heterogeneity of enhancement on post-contrast T1-weighted images.

## Materials and methods

### Patients

This study was approved by the local medical ethics committee. Between January 2002 and December 2006 a series of 44 consecutive patients [mean age was 61 years (range: 40–86 years); 11 women and 33 men] with a HNSCC who underwent a unilateral or bilateral supra-omohyoid neck dissection (SOHND) (dissection of levels I-III) or radical (modified) neck dissection [R(M)ND] (dissection of levels I-V) was studied. All patients underwent MR imaging as part of the routine diagnostic workup. This was performed on a 1.5-T machine (Gyrosan, Powertrack 6000, Philips, Best, The Netherlands) by using a head-neck coil (Philips, Best, The Netherlands). Table 1 presents the relevant parameters of the MRI protocol.

### MR evaluation

One general radiologist (observer 1) and one radiologist specialized in head and neck imaging (observer 2) independently evaluated the MR images retrospectively. Both observers were blinded to each other's MR assessments, clinical information, and the results of the histological examination.

**Table 1** Parameters of the head and neck MRI protocol

Parameters	Sequences			
	TSE T1-weighted	SPIR <sup>a</sup> TSE T2-weighted	SPIR CE <sup>b</sup> T1-weighted	SPIR CE T1-weighted
Field of view (mm)	220	220	220	220
Slice orientation	Transverse	Transverse	Coronal	Transverse
Matrix	512	512	512	513
Section thickness (mm)	3	3	3	3
No. of sections	65	65	50	65
No. of signals acquired	3	3	3	3
Acquisition time (min:s)	5:37	5:09	6:05	6:40
TSE <sup>c</sup> factor	3	20	4	4
TE <sup>d</sup> (ms)	13	80	14.50	14.50
TR <sup>e</sup> (ms)	530	Shortest	500	500
Slice gap	0	0	0	0

<sup>a</sup>SPIR spectral pre saturation inversion recovery

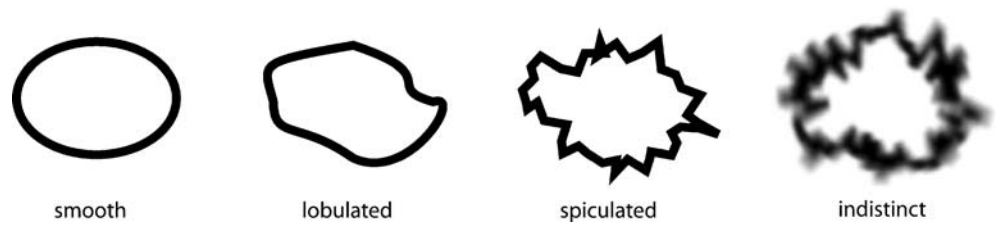
<sup>b</sup>CE contrast enhanced

<sup>c</sup>TSE turbo spin echo

<sup>d</sup>TE echo time

<sup>e</sup>TR repetition time

**Fig. 1** Schematic drawing of the four borders for assessment of lymph nodes

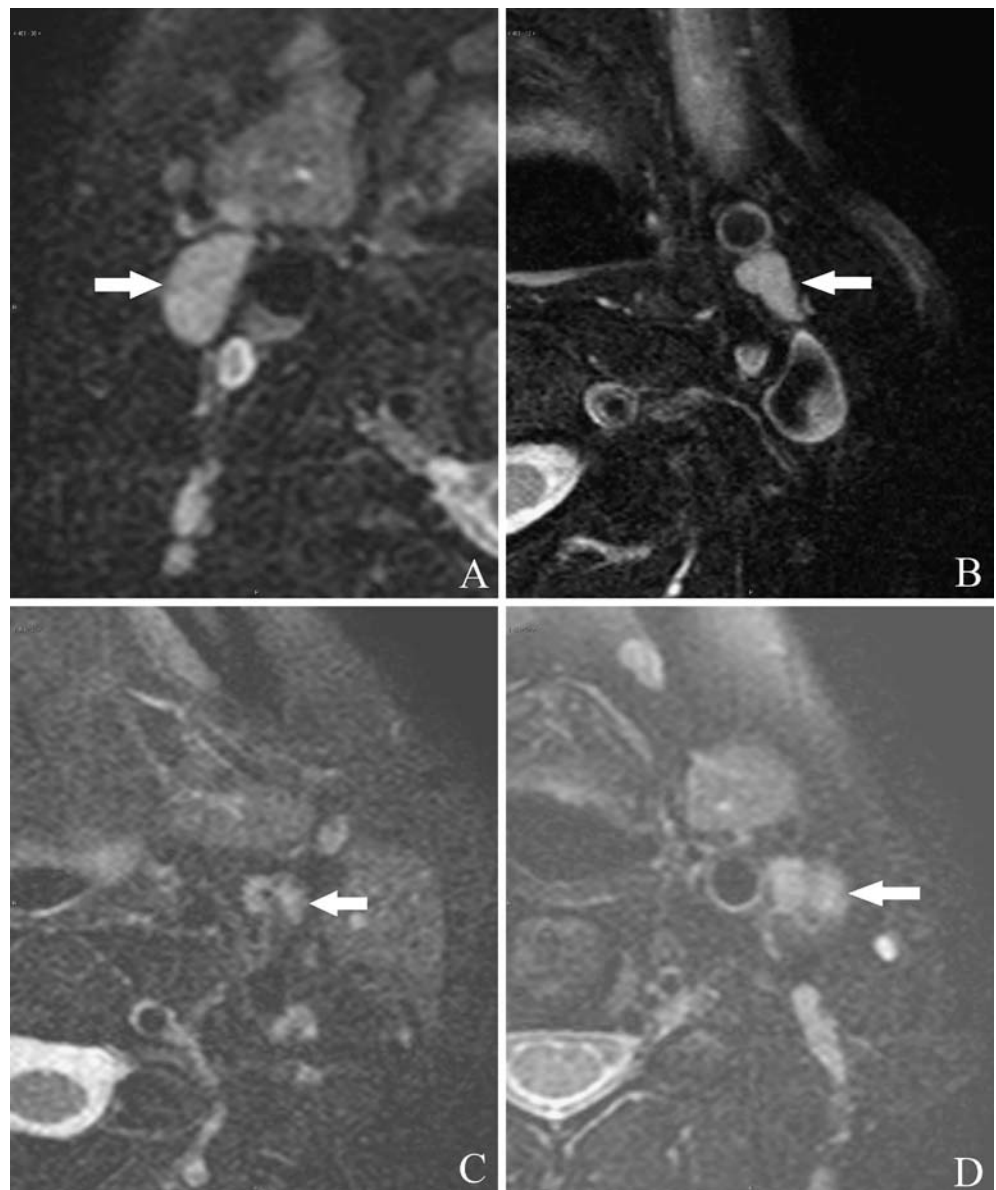


In the first session, all lymph nodes were determined by position and slice number per neck level. The short axial diameter was recorded per lymph node. All lymph nodes were classified as normal ( $\leq 10$  mm) or malignant ( $>10$  mm).

After a time interval of 8 weeks, the same MR images were reviewed again by the same radiologists blinded to

each others' MR assessments, clinical information, and the results of the histological examination. For every lymph node the decision was made whether it was normal or metastatic using three morphologic criteria. The first criterion was border as observed on fat-suppressed T2-weighted images (smooth, lobulated, spiculated, indistinct) (Fig. 1 demonstrates the four different borders on the

**Fig. 2** Transverse turbo spin-echo T2-weighted images of the neck. Examples of the four different scores on border regularity. The lymph nodes (arrows) show (A) a smooth border, (B) a lobulated border, (C) a spiculated border, and (D) an indistinct border



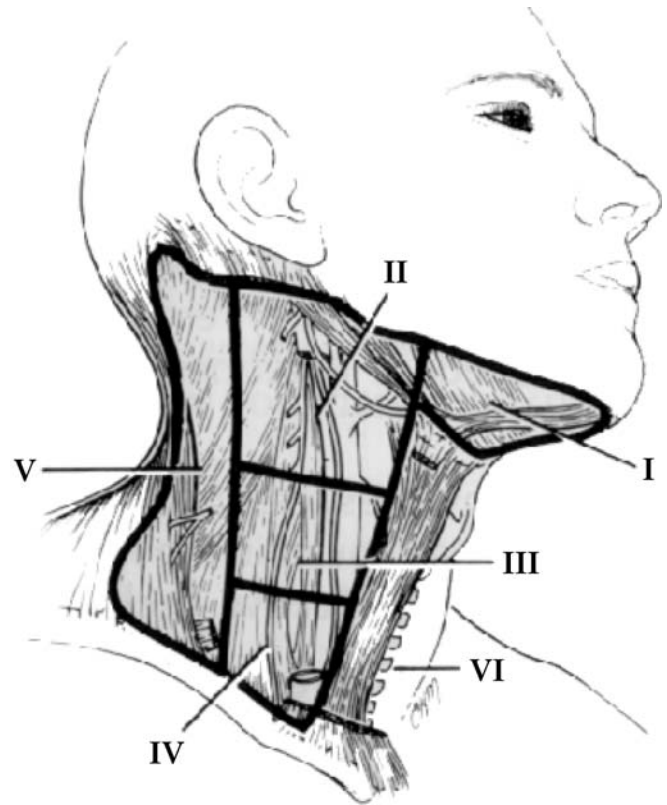
schematic drawing). Smooth (Fig. 2A) and lobulated (Fig. 2B) borders were considered as indicative of normal lymph nodes. Spiculated (Fig. 2C) and indistinct (Fig. 2D) borders were considered as indicative of metastatic lymph nodes. The second criterion was degree of homogeneity of the signal intensity on contrast-enhanced T1-weighted images. A homogeneous enhancement was considered as normal. A heterogeneous enhancement was considered as indicative of metastatic lymph nodes. The third criterion was degree of homogeneity of the signal intensity on T2-weighted images. A homogeneous signal intensity was considered as normal. A heterogeneous signal intensity was considered as indicative of metastatic lymph nodes (Fig. 3).

### Pathological examination

All neck dissections were performed en bloc. Immediately after the resection, the surgeon positioned the neck dissection specimen on a schematic drawing of the neck in real proportions and fixed it with needles (Fig. 4). The pathologist manually identified and localized the lymph nodes per neck level in the specimen. The short axial diameter of all lymph nodes was recorded. Subsequently, lymph nodes were fixed, sectioned, and hematoxylineosine (HE) stained, and the presence of tumor in each lymph node was examined microscopically. The pathological results were used as the reference standard.



**Fig. 3** Transverse turbo spin-echo T2-weighted image of the neck showing an example of heterogeneous signal intensity (SI) in a lymph node in level II on the right side. The lymph node (arrowhead) with a homogenous SI, although a short axial diameter of 13 mm, showed no metastasis, whereas the smaller lymph node (arrow) (short axial diameter 9 mm) with a heterogeneous and eccentric area of low SI (small arrow) revealed metastasis at the pathologic examination



**Fig. 4** Schematic drawing of the different levels in the neck

### Matching MR assessment to pathological examination

The neck was subdivided according to the six different levels in agreement with the classification of the American Joint Committee on Cancer (AJCC); this classification was used by the radiologists when viewing the MR images and used by the pathologist when interpreting the specimen after neck dissection [23].

The results of the measurements on MRI were compared with the results of the pathologic examination of the neck dissection specimens. By recording the combination of the short axial diameter and the exact location of each lymph node, it was possible to perform a topographical correlation for each lymph node per neck level.

### Statistical analysis

Inter-observer agreement with respect to the evaluation of the criterion nodal size, and the criteria border irregularity, homogeneity of contrast enhancement on T1-weighted images, and homogeneity of signal intensity on T2-weighted images was expressed by Cohen's kappa coefficient ( $\kappa$ ).

For each lymph node, the scores for the MRI criteria were correlated with the outcome of the histological



examination of the neck dissection specimen: presence or absence of lymph node metastasis. Diagnostic performances of nodal size and the new criteria for the diagnosis of metastasis were evaluated using diagnostic parameters, such as sensitivity, specificity, and diagnostic odds ratio (DOR). In diagnosis, one always has to compromise between sensitivity and specificity: as sensitivity increases, specificity will decrease and vice versa. The DOR is a measure of diagnostic performance, which incorporates sensitivity and specificity and thus captures the trade-off between these measures. A DOR=1 indicates that the test under study has no diagnostic value; a DOR>1 indicates that the test under study (in this case, the new MRI criteria) has the ability to discriminate between lymph nodes with and without metastasis. The larger the DOR is, the larger the discriminative ability [24].

Multivariate logistic regression analysis was used to evaluate whether a criterion, when used in combination with the other criteria, can be used as an independent indicator for differentiating metastatic from non-metastatic lymph nodes. The independent contribution of each criterion to the diagnostic performance is expressed as the DOR, which can be derived by exponentiation of the corresponding regression coefficient, where 95% confidence intervals (95% CI) are used to indicate whether the DOR is significantly different from DOR=1. Multivariate logistic regression analysis was also used to examine which of the new MRI criteria were most predictive of the presence of metastases and whether the use of these new criteria in addition to size significantly improved the detection of cervical lymph nodes metastases in HNSCC.

The dependent variable in these models was the presence or absence of metastasis according to the pathological examination. The models incorporated as independent variable size as well as the three new MRI criteria. All criteria were entered as dichotomous variables, where abnormal and normal results were coded as 1 and 0, respectively.

Predicted probabilities of metastasis from these models were used to calculate the area under the curve (AUC) with 95% CI as measure of diagnostic performance. The AUC of the model incorporating both the new criteria and the size criterion was compared with the AUC of the model that incorporated only the size criterion. The difference in AUCs for the different models was tested using the method described by Hanley et al., which accounts for the fact that the AUCs are derived from the same sample of patients [25]. A p-value <0.05 was considered to be statistically significant.

## Results

In 44 patients a neck dissection was performed: 9 supraomohyoid neck dissections and 37 radical (modi-

fied) neck dissections (in 2 patients a bilateral neck dissections). Distribution of the dissected neck levels was as follows; 32 level I, 41 level II, 34 level III, 25 level IV, and 8 level V.

At pathological examination a total of 261 lymph nodes was found: 71 lymph nodes with metastasis and 190 without metastasis (prevalence=27.2%). In all levels together, a total of 111 lymph nodes was found in level II, 52 lymph nodes in level I, 65 lymph nodes in level III, 25 lymph nodes in level IV, and 8 lymph nodes in level V. Lymph node metastases were present in 33 patients (patient prevalence=80.5%). The majority (82%) of 261 assessed lymph nodes was scored as having a size <10 mm. The average pathologic yield per patient was 11.5 lymph nodes.

At assessment of the MR images of the dissected neck levels, a total of 360 lymph nodes was detected. Of these lymph nodes, 99 were shown to have a short axial diameter of  $\leq 3$  mm. Because these lymph nodes were not detected at pathological examination, they were excluded from further analysis.

A total of 261 lymph nodes, which was found at pathological examination, was matched to lymph nodes that were detected on MRI by the two observers.

For observer 1, scores were lacking in 1 lymph node metastasis, leaving 260 lymph nodes for analysis: 70 lymph nodes with metastasis and 190 without metastasis. For observer 2, complete data were available for all 261 lymph nodes.

Observer agreement was  $\kappa=1.00$  for size,  $\kappa=0.62$  for border irregularity,  $\kappa=0.51$  for signal intensity on contrast-enhanced T1-weighted images, and  $\kappa=0.51$  for signal intensity on T2-weighted images.

Table 2 shows the sensitivity, specificity, and diagnostic odds ratio (DOR) with 95% confidence interval (95% CI) for the diagnosis of metastasis for the criteria border (abnormal versus normal) on T2-weighted images, signal intensity on contrast-enhanced T1-weighted images (heterogeneous versus homogeneous), and signal intensity on T2-weighted images (heterogeneous versus homogeneous) for the two observers. With respect to the new criteria, the highest DORs are found for border irregularity and signal intensity on T2-weighted images. The lowest DORs are found for the criterion contrast enhancement on T1-weighted images.

Table 3 shows the results for lymph nodes that were smaller than 10 mm. The DORs associated with the new criteria are smaller compared to the DORs for all lymph nodes, but are still elevated, indicating that the morphologic criteria are also useful for the detection of metastases in small lymph nodes.

Table 4 shows the results from multivariate logistic regression analyses. The DORs associated with border irregularity were 2.61 (95% CI: 1.12–6.08) and 66.2 (95% CI: 20.4–217) for observer 1 and 2, respectively; for heterogeneity on T2-weighted images DORs were 2.97 (95% CI: 1.42–6.18) and 22.6 (95% CI: 6.40–80.1). The DORs associated with heterogeneity on T1-weighted images are not significantly different from DOR=1. Another observation was that for observer 2, the DOR

**Table 2** Sensitivity, specificity, and diagnostic odds ratio (DOR) with 95% confidence interval (95% CI) for the diagnosis of metastasis for the MR criteria: size, border irregularity, signal intensity (SI) on contrast-enhanced (CE) T1-weighted images and SI on T2-weighted images for all lymph nodes

All lymph nodes	Observer 1			Observer 2		
	Sensitivity	Specificity	DOR (95% CI)	Sensitivity	Specificity	DOR (95% CI)
Short axial diameter (mm) >10 versus ≤10	43	92	8.16 (4.09–16.3)	42	92	7.96 (3.99–15.9)
Borders on T2-weighted images spiculated/indistinct versus smooth/lobulated	63	84	8.68 (4.69–16.1)	87	94	112 (44.7–280)
SI on CE T1-weighted images heterogeneous versus homogeneous	71	66	4.81 (2.65–8.71)	61	65	2.89 (1.65–5.05)
SI on T2-weighted images heterogeneous versus homogeneous	67	77	6.99 (3.83–12.7)	93	68	28.6 (11.3–72.3)

associated with size was 1.02, indicating that for this observer size had no additional diagnostic value when considered in combination with the other criteria.

The AUCs for predictive models using size only (≤10 mm versus >10 mm) were 0.67 (95% CI: 0.61–0.73) and 0.68 (95% CI: 0.62–0.74) for observer 1 and 2, respectively. After incorporation of the three new criteria into models, the AUCs increased significantly to 0.81 (95% CI: 0.75–0.87) for observer 1 and to 0.96 (95% CI: 0.94–0.98) for observer 2 ( $p < 0.001$ ). When the criterion “homogeneity of the signal intensity on contrast-enhanced T1-weighted images” was omitted from the predictive model, there was only a very small decrease in AUC for observer 1 from 0.81 to 0.79 (95% CI: 0.73–0.85) and remained 0.96 (95% CI: 0.93–0.98) for observer 2. This observation indicates that this criterion has little added diagnostic value.

## Discussion

The principal finding of this study was that in addition to the size criterion, new criteria, such as border irregularity and heterogeneity on T2-weighted images, result in a better diagnostic performance of MRI for the detection of cervical lymph node metastases in HNSCC.

Accurate assessment of cervical lymph node metastases in HNSCC is important regarding prognosis and choice of

management. Detection of lymph node metastases is usually based on the short axial diameter as size criterion. However, many studies have shown that the size criterion alone was not accurate enough as predictor for lymph node metastasis [16]. Sensitivity is poor when the commonly chosen cutoff value of 10 mm is used, and although use of a lower cutoff value, as proposed by van den Brekel et al., results in higher sensitivity, lower cutoff values are associated with low specificity [26]. We evaluated in this study the effect on sensitivity and specificity when lowering the cutoff point from 10 to 7 mm in short axial diameter; sensitivity raised from 43% to 79%, but the associated specificity expectedly lowered from 92% to 64%. However, the corresponding diagnostic odds ratios (DORs) did not differ significantly (DOR=8.16 with 95% CI 4.09–16.3 versus DOR=6.43 with 95% CI 3.38–12.23). Another assessment of lymph node dimensions is the measurement of ratios of maximum longitudinal to maximum short axial diameter (l/s ratio). A ratio less than 2, like in round lymph nodes versus elliptical lymph nodes, is indicative of metastatic disease, but this is related to enlarged lymph nodes. Because in our presented series 82% of all assessed lymph nodes were not enlarged – showing short axial diameters less than 10 mm – we used in this study the 10-mm short axial diameter as cutoff point.

Additional morphological criteria for the detection of lymph node metastasis have been evaluated in this study:

**Table 3** Sensitivity, specificity, and diagnostic odds ratio (DOR) with 95% confidence interval (95% CI) for the diagnosis of metastasis for the MR criteria: size, border irregularity, signal intensity (SI) on contrast-enhanced (CE) T1-weighted images and SI on T2-weighted images for lymph nodes <10 mm in short axial diameter

Lymph nodes <10 mm	Observer 1			Observer 2		
	Sensitivity	Specificity	DOR (95% CI)	Sensitivity	Specificity	DOR (95% CI)
Borders on T2-weighted images spiculated/indistinct versus smooth/lobulated	40	87	4.61 (2.12–9.99)	78	97	99.6 (33.1–299)
SI on CE T1-weighted images heterogeneous versus homogeneous	53	70	2.52 (1.25–5.08)	42	68	1.49 (0.74–3.00)
SI on T2-weighted images heterogeneous versus homogeneous	53	79	4.24 (2.06–8.71)	88	68	15.6 (5.70–41.8)

**Table 4** Results of multivariate logistic regression analyses. Regression coefficients ( $\beta$ ), diagnostic odds ratios (DOR) with 95% confidence intervals (95% CI) for the size criterion, and the three new assessed MR criteria border, signal intensity (SI) on contrast-enhanced (CE) T1-weighted images and T2-weighted images for both MR observers

MRI criteria	Observer 1		Observer 2	
	$\beta$	DOR (95% CI)	$\beta$	DOR (95% CI)
Size >10 versus $\leq$ 10 mm	1.06	2.89 (1.25–6.70)	0.02	1.02 (0.25–4.18)
Border on T2-weighted images spiculated/indistinct versus smooth/lobulated	0.96	2.61 (1.12–6.08)	4.20	66.2 (20.4–217)
SI on CE T1-weighted images heterogeneous versus homogeneous	0.37	1.45 (0.67–3.14)	0.68	1.97 (0.70–5.59)
SI on T2-weighted images heterogeneous versus homogeneous	1.09	2.97 (1.42–6.18)	3.12	22.6 (6.40–80.1)

the degree of border irregularity on T2-weighted images, homogeneity of the signal intensity on contrast-enhanced T1-weighted images, and the homogeneity of the signal intensity on T2-weighted images of lymph nodes.

The results of univariate analyses, with which we compared the diagnostic performance of all four criteria under study, indicate that all criteria, when used alone, help to discriminate between lymph nodes with and without metastasis, but that the discriminative ability was lowest for degree of homogeneity of signal intensity on contrast-enhanced T1-weighted images. This finding also holds after restricting the analysis to lymph nodes smaller than 10 mm. However, when compared with the analysis involving all lymph nodes, DORs were lower, indicating that within small nodes the discriminative ability is poorer. An exception was border irregularity, which for observer 2 was still associated with a high DOR of about 100 (compared with a DOR of 112 in the analysis based on all lymph nodes).

Another morphological criterion that has been used is the presence of central necrosis. However, central necrosis is often seen in the larger involved lymph nodes, which based on their size only would have been classified as malignant anyhow [17–20]. The majority of lymph nodes in our series (82%) showed subcentrimetrical short axial diameters.

Curtin et al. have already described the diagnostic value of the appearance of internal abnormalities in lymph nodes on CT and MRI; however, the performance of MRI was not changed significantly by the addition of information on internal abnormalities [18].

Evaluation of the results of multivariate logistic regression analysis indicates that, if used in combination with the size criterion, for both observers the scores on border irregularity and heterogeneous signal intensity on T2-weighted images contribute significantly to the prediction of the presence of metastatic lymph nodes, whereas the criterion heterogeneity of signal intensity on contrast-enhanced T1-weighted images has no additional diagnostic value.

Explanations for the MR features in metastatic lymph nodes could be the following. Firstly, changes of a smooth or lobulated border of normal lymph nodes into a spiculated or indistinct border could be due to direct extra-nodal tumor infiltration into the peri-nodal fatty tissue. Secondly, this phenomenon could be explained by a desmoplastic reaction around the affected lymph node, the

similar feature that can be observed around a primary tumor site. Thirdly, tumor infiltration and presence of softening or necrosis within lymph nodes usually show on the pathological examination an irregular and heterogeneous pattern. This architectural distortion of the nodal parenchyma results in an irregular signal intensity on T2-weighted images and in a heterogeneous signal intensity on the contrast-enhanced T1-weighted images.

The discrepancies in diagnostic performance between the two observers and low inter-observer agreement regarding the new morphological criteria could be explained by the fact that observer 2, experienced in head and neck radiology, was better aware of the diagnostic value of border irregularity and homogeneity of signal intensity than his colleague who had less experience in the assessment of lymph node involvement. In this respect, the results also show that the criterion size for lymph nodes has limited discriminative value for the experienced observer 2. For the more experienced observer, border irregularity and heterogeneity of signal intensity on T2-weighted images are more decisive in the diagnosis. This is reflected by the results of the univariate analysis with high DORs for the criteria border and signal intensity on T2-weighted images (112 and 28.6, respectively), when compared with the low DOR for the size criterion (7.96). Also, in the multivariate logistic regression analysis high DORs are presented for those criteria (66.2 and 22.6, respectively). This is in contrast to the DOR of 1.02 for the size criterion.

## Conclusion

Newly assessed morphological criteria like border irregularity and heterogeneity of signal intensity on T2-weighted images in addition to size significantly improved the detection of cervical lymph node metastases on MRI in patients with HNSCC.

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