

# Depth of invasion determined by MRI in cT1N0 tongue: is it an indicator for elective neck dissection?

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## Research article

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# Abstract

**Abstracts Background** Depth of invasion (DOI) could be calculated by MRI preoperatively, whether MRI-determined DOI could predict the prognosis and whether it could be used as an indicator for neck dissection for cT1N0 tongue squamous cell carcinoma (SCC) remain unknown, the main goal of the current study aimed to answer the questions. **Methods** Patients with surgically treated cT1N0 tongue SCC were retrospectively enrolled, MRI-determined DOI was measured based on T1-weighted layers by a 1.5T scan. A multivariate logistic regression analysis model was used to determine the independent predictors for occult neck lymph node metastasis. The main study endpoints were locoregional control survival (LRC) and disease specific survival (DSS), the Cox model was used to determine the independent prognostic factors for the LRC and DSS. **Results** Occult neck lymph node metastasis was noted in 26 (17.2%) patients, ROC curve indicated the optimal cutoff value of MRI-determined DOI was 7.5mm for predicting neck lymph node metastasis with sensitivity of 86.9%. The factors of lymphovascular invasion, MRI-determined DOI, pathologic DOI, and pathologic tumor grade were significantly associated with the presence of neck lymph node metastasis in univariate analysis, further logistic regression analysis confirmed the independence of lymphovascular invasion, MRI-determined DOI, and pathologic DOI in predicting the neck lymph node metastasis. The 5-year LRC and DSS rates were 84% and 90%, respectively. Cox model analysis suggested the MRI-determined DOI was an independent prognostic factor for both the LRC and DSS. **Conclusions** Elective neck dissection is suggested if MRI-determined DOI is greater than 7.5mm in cT1N0 tongue SCC, and MRI-determined DOI  $\geq$ 7.5mm indicates more risk for disease recurrence and cancer caused death.

## Background

Neck lymph node metastasis is one of the most important prognostic factors in tongue squamous cell carcinoma (SCC) [1], but unfortunately these positive lymph nodes are usually occult or subclinical at the initial treatment in early stage tongue SCC. Owing to a wide range of occult metastasis rate [2, 3], either elective neck dissection (END) or the watchful waiting policy has been the favored treatment for cT1N0 tongue SCC [4, 5]. Investigators favoring for END comment that END allows more accurate disease stage and decision of the need for adjuvant therapies, and resection of metastatic lymph nodes could potentially reduce the recurrence risk [6, 7], however, the main concern according to the traditional watchful waiting policy is the associated surgical complication including shoulder dysfunction and over-treatment for those patients having no pathologic metastases [8]. Considering there is no accurate diagnostic procedure for staging the neck preoperatively, the elective management of the neck in cT1N0 tongue SCC has been the subject of much debate during the past 3 decades and continues to be controversial.

Depth of invasion (DOI) is now added in the newest edition of AJCC tumor-node-metastasis staging system [9], and abundant literature has showed the significant relationship between DOI and neck lymph node metastasis [10-12], however, data regarding pathologic DOI usually can not be obtained by frozen section or incisional biopsy, it might has limited role on benefiting decision making of neck treatment

preoperatively. MRI has been widely used to evaluate the soft tissue disease, and current evidence has reported the reliability of MRI in measuring the DOI [13, 14] as well as the prognostic value of MRI-determined tumor thickness in tongue SCC [15, 16], the MRI-determined DOI is significantly different from the MRI-determined tumor thickness, but whether MRI-determined DOI has the same effect with the MRI-determined tumor thickness and whether it could be used as an indicator for END for cT1N0 tongue SCC remain unknown, therefore, the main goal of current study was to clarify these questions.

## Patients and methods

The Zhengzhou University Institutional Research Committee approved our study, and all patients signed informed consent agreements for medical research before initial treatment. All methods were performed in accordance with the relevant guidelines and regulations.

From January 2010 to December 2016, medical records of adult ( $\geq 18$  years) patients with surgically treated tongue SCC were reviewed. Enrolled patients must meet the following criteria: the disease must be primary; the disease was re-staged as cT1N0M0 according to the 7<sup>th</sup> AJCC classification followed by examinations of ultrasound, CT, and MRI; Data regarding MRI could be obtained; data regarding the follow-up could be obtained. Information including age, sex, tumor growth pattern, adverse pathologic characteristics, and follow-up of enrolled patients was extracted and analyzed.

MRI-determined DOI was measured based on T1-weighted layers by a 1.5T scan [13, 14], it was defined as the vertical distance between the deepest point of tumor infiltration and the simulated normal mucosal junction (Figure 1). For exogenous tumors, the part above the mucosal surface was neglected, and for ulcerative tumors, the invaginated part was added [17]. The MRI-determined DOI was measured by at least two radiologists.

All pathologic sections were re-reviewed by at least two pathologists, and perineural invasion was considered to be present if tumor cells were identified within the perineural space and/or nerve bundle; lymphovascular infiltration was positive if tumor cells were noted within the lymphovascular channels [18]. The pathologic DOI was measured from the level of the adjacent normal mucosa to the deepest point of tumor infiltration, regardless of the presence or absence of ulceration [9].

In our cancer center, END (level $\bar{X}$ - $\bar{X}$ ) was routinely performed for tongue SCC patients with the exception of very early-stage disease. Primary tumor excision was usually performed without lip-splitting, the mouth floor tissue was usually preserved unless there was lingual lymph node metastasis reported by frozen section. After therapy, the patients were examined every 3 months during the first year, every 6 months during the second year, and once per year after the second year [1]. Once there was doubt of disease recurrence, aspiration biopsy or incisional biopsy combined other examinations were performed.

The MRI-determined and pathologic DOI was compared using the pair student t test. The ROC curve was used to determine the optimal cutoff of the MRI-determined DOI for predicting the neck lymph node metastasis. The Chi-square test was used to evaluate the association between clinical pathologic

variables and neck lymph node metastasis, the factors which were significant in the Chi-square test were then analyzed in a multivariate logistic regression analysis model to determine the independent predictors. The primary outcome was locoregional control survival (LRC) and disease specific survival (DSS), the survival time of LRC was calculated from the date of surgery to the date of local or regional recurrence or the last follow-up, and the survival time of DSS was calculated from the date of surgery to the date of cancer-caused death or the last follow-up. The Kaplan-Meier method (log-rank test) was used to calculate the LRC and DSS rates. The factors which were significant in univariate analysis were then analyzed in the Cox model to determine the independent prognostic factors. A value of  $p < 0.05$  was considered significant, and all statistical analyses were performed with SPSS 20.0.

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## Results

There were 151 patients (111 male and 40 female) enrolled in total, the mean age was 57.1 (range: 30-78) years. There were 102 (67.5%) smokers and 61 (40.4%) drinkers, respectively. Flap reconstruction was performed in 32 (21.2%) patients including 25 submental island flaps and 7 radial forearm flaps. Perineural invasion and lymphovascular invasion were presented in 23 (15.2%) and 19 (12.6%) patients, respectively. Pathologic tumor grades were distributed as low in 75 patients, intermediate in 51 patients, and high in 25 patients. Negative margin was achieved in all patients. Tumor growth patterns of ulcer type, invasive type, and exogenous type were noted in 72 (47.7%), 20 (13.2%), and 59 (39.1%) patients, respectively.

Positive neck lymph nodes were noted in 26 (17.2%) patients, there was one positive lymph node in 15 patient, two positive lymph nodes in 7 patient, and three positive lymph nodes in 4 patients. There was no extracapsular spread in all the positive lymph nodes.

The mean MRI-determined and pathologic DOI was 6.9 (range: 2-13) mm and 4.2 (range: 1.0-10.0) mm, respectively, the difference was significant ( $p < 0.001$ ).

ROC analysis described the optimal cutoff value of MRI-determined DOI was 7.5mm for predicting neck lymph node metastasis with the area under the curve being 0.848; specificity: 82.0%; sensitivity: 86.9% (Figure 2).

As described in Table 1, the factors of lymphovascular invasion ( $p = 0.015$ ), MRI-determined DOI ( $p = 0.007$ ), pathologic DOI ( $p = 0.008$ ), and pathologic tumor grade ( $p = 0.034$ ) were significantly associated with the presence of neck lymph node metastasis, further logistic regression analysis confirmed the independence of lymphovascular invasion ( $p = 0.022$ , 2.475 [1.233-4.997]), MRI-determined DOI ( $p = 0.009$ , 2.978 [1.574-7.332]), and pathologic DOI ( $p < 0.001$ , 3.112 [1.812-9.668]) in predicting the neck lymph node metastasis.

During our follow up with mean time of 70.4 (range: 8-103) months, 30 patients underwent adjuvant radiotherapy, 6 patients also underwent adjuvant chemotherapy. Locoregional recurrence occurred in 22 patients, disease-caused death occurred in 13 patients.

The 5-year LRC rate was 84%. With regard to prognostic factors for the LRC, as described in Table 2, the factors of perineural invasion ( $p=0.016$ ), lymphovascular invasion ( $p=0.009$ ), MRI-determined DOI ( $p<0.001$ ), pathologic DOI ( $p<0.001$ ), and neck lymph node metastasis ( $p=0.004$ ) were significantly related to the LRC. Further cox model indicated the independence of lymphovascular invasion ( $p=0.016$ , 2.007 [1.274-5.732]), MRI-determined DOI ( $p<0.001$ , 2.842 [1.449-7.264]), neck lymph node metastasis ( $p=0.035$ , 1.745 [1.152-4.221]) and pathologic DOI ( $p<0.001$ , 3.246 [1.679-8.336]) in predicting the LRC. In patients with MRI-determined DOI  $\geq 7.5$ mm, the 5-year LRC rate was 68%, in patients with MRI-determined DOI  $< 7.5$ mm, the 5-year LRC was 90%, the difference was significant (Figure 3,  $p<0.001$ ).

The 5-year DSS rate was 90%. With regard to prognostic factors for the DSS, as described in Table 3, the factors of MRI-determined DOI ( $p<0.001$ ), pathologic DOI ( $p<0.001$ ), and neck lymph node metastasis ( $p=0.008$ ) were significantly related to the LRC. Further cox model indicated the independence of MRI-determined DOI ( $p<0.001$ , 2.441 [1.635-5.994]), pathologic DOI ( $p<0.001$ , 3.002 [1.753-6.885]), and neck lymph node metastasis ( $p=0.005$ , 2.665 [1.442-5.322]) in predicting the DSS. In patients with MRI-determined DOI  $\geq 7.5$ mm, the 5-year DSS rate was 73%, in patients with MRI-determined DOI  $< 7.5$ mm, the 5-year LRC was 96%, the difference was significant (Figure 4,  $p<0.001$ ).

## Discussion

The most valuable finding in current study was that MRI-determined DOI was significantly associated with the presence of neck lymph node metastasis, it would add nearly 3-fold risk of neck lymph node metastasis if MRI-determined DOI was greater than 7.5mm, and MRI-determined DOI was an independent prognostic factor for the LRC and DSS. The finding might provide preoperative benefit in neck management in cT1N0 tongue SCC.

The feasibility of measurement of DOI by MRI has been widely analyzed [13, 14, 16, 17]. Murakami et al. [13] compared the inter-rater reliability of different methods of DOI measurement by MRI, the authors found the method of the axial invasive portion had excellent inter-rater reliability. The data in current study was also obtained by the axial invasive portion. Lam et al.[19] described that the tumor thickness measured on T1-sequence MRI was 0.8 mm greater than that measured in pathological sections, but 2 mm greater on T2 sequences than that measured in pathological sections on average. Similar finding was also noted by Preda et al.[20]. T1-weighted images were more accurate for measuring the DOI than T2 sequences. DOI in T2 weighted images could be overestimated owing to the inflammation and surround tissue edema. Therefore, in current study, the MRI-determined DOI was obtained based on T1 sequences to increase our reliability. In the other hand, Park et al.[14] reported compared to the data measured in postoperative pathological sections, the DOI on T1 MRI was 1.5 mm greater, but the mean difference between MRI-determined DOI and pathologic DOI was 2.7mm in current study, a little greater

than previous finding [14, 19, 20], possible explanation was that only staged T1 tumors were included for analysis, relatively higher extent of tissue shrink existed in smaller tumors.

The presence of neck lymph node metastasis was an important prognostic factor for head and neck SCC [1, 3]. END was usually an important part in primary operation, but owing to the wide range of occult metastasis rate in cT1N0 tongue SCC [7], the neck management of cT1N0 tongue SCC has been debated over the years remaining its controversy. The ideal treatment for patients with cT1N0 tongue SCC must be balanced between and the possible surgical morbidity and optimal oncological outcomes. The common principle was that N0 necks should be treated electively when the occult metastatic rate was more than 20% [11, 21]. In current study, the overall occult metastasis rate was 17.2%, but all patients underwent END. There were at least three aspects for explaining this phenomenon: firstly, the high requirement of routine follow-up of wait-and-see policy was usually out of our patients' ability, as described by our previous studies [22, 23], patients in our cancer hospital usually came from low income family and remote districts; secondly, there was abundant evidence indicating that there was often a low salvage rate on disease recurrence in patients who do not have prophylactic therapy of the clinically N0 neck [2-5], thirdly, also the most important one, there were no reliable predictors for occult neck lymph node metastasis from previous studies.

A number of researchers had aimed to explore the potential predictors for the occult neck lymph node metastasis. Tumor budding was defined as the presence of small clusters of cancer cells or isolated single cancer cell, it suggested a more aggressive biologic behavior and carried more possibility of migrating to the adjacent stroma. Xie et al.[24] described the tumor budding intensity was significantly associated with occult lymph node metastasis. Systemic inflammatory response could promote tumor cell proliferation, microvascular regeneration, and tumor metastasis, further, the peripheral neutrophil-to-lymphocyte ratio (NLR) was an accurate and reliable inflammatory marker. High NLR is thought to be significantly associated with worse survival in solid cancers [25]. Abbate et al.[26] firstly presented there was higher risk for occult neck lymph node metastasis when pre-treatment NLR was greater than 2.93. Loganathan et al.[27] recently reported END should be considered when the tumor thickness exceeds 5 mm based on the significant relationship between tumor thickness and occult neck lymph node metastasis. Other analyzed variables included perineural invasion, lymphovascular invasion, and pathologic DOI [28, 29]. However, data regarding the pathologic factors usually could not be obtained preoperatively, and pretreatment NLR were nonspecific parameters because they could be influenced by concomitant conditions, such as infections or inflammation. Therefore, more accurate indicators were needed.

As discussed as above, MRI-determined DOI could be reliably calculated preoperatively, and our result presented high predictive value of MRI-determined  $DOI \geq 7.5\text{mm}$  in identifying occult metastasis with sensitivity of 86.9%. In another study by Jung et al.[30], the authors recommended a cut-off value of 10.5 mm in contrast-enhanced T1-weighted images and showed a significant correlation with nodal metastasis, but the authors failed to give the information about the sensitivity, and the variation from ours could be explained by the different calculation method of the cut-off value. The potential

mechanism for our interesting finding was presented as follows: MRI-determined DOI could indirectly reflect the pathologic DOI, mean difference between MRI-determined DOI and pathologic DOI was 2.7mm in current study, therefore, a MRI-determined DOI cut-off value of 7.5mm would be indicating a pathologic DOI cut-off value of 5.0mm, extensive literature had reported the neck lymph node metastasis risk increased apparently if there was pathologic DOI >5.0mm [10, 11, 28, 29].

Prognostic factors for tongue SCC had been extensively analyzed, widely accepted risk factors included disease stage, tumor differentiation, perineural invasion, lymphovascular invasion, neck lymph node status, pathologic DOI, and so on [1, 12, 16, 23, 27, 31]. Similar finding was also noted in current study. But the significance of MRI-determined DOI in the survival of tongue SCC remained unknown, this was the first study to describe a significant association between MRI-determined DOI and the prognosis, MRI-determined DOI  $\geq$  7.5mm mean higher risk of disease recurrence and cancer-caused death. The potential mechanism might be explained by that greater MRI-determined DOI indicated greater pathologic DOI, the negative affect of pathologic DOI on the prognosis had been widely suggested. Tam et al.[12] recently reported the DOI was an independent predictor for both overall survival and DSS. Similar finding was also presented by Iida et al.[32] and Jung et al.[30].

Almost all the literature regarding MRI-determined DOI is just focused on evaluating the association between MRI-determined DOI and pathologic DOI, we hope the current research could provide assistance in neck management in patients with cT1N0 tongue SCC and looking for better ways to analyze and control its progression.

Limitation of this study must be acknowledged: firstly, there was inherent bias in a retrospective study. Second, the sample size was relatively small, possibly reducing the statistical power, therefore, larger sample-size studies were needed to clarify the question.

In summary, there is significant relationship between MRI-determined DOI and occult neck lymph node metastasis in cT1N0 tongue SCC, elective neck dissection is suggested if MRI-determined DOI is greater than 7.5mm, and MRI-determined DOI  $\geq$  7.5mm indicates more risk for disease recurrence and cancer caused death.

## Abbreviations

LRC: locoregional control survival;

SCC: squamous cell carcinoma;

DOI: depth of invasion;

DSS: disease specific survival;

## Declarations

## Ethics approval and consent to participate

The Zhengzhou University institutional research committee approved our study and all participants signed an informed consent agreement for medical research before initial treatment. And all the related procedures were consistent with Ethics Committee regulations.

**Consent to publish**All the material came from our cancer center, and the publish consent have been obtained from all the patients.**Availability of data and materials**

All data generated or analyzed during this study are included in this published article. And the primary data could be achieved from the corresponding author.

**Competing interests**The authors declare that they have no competing interests.**Funding**This study was not funded by any outside source.**Authors' Contributions**

Study design and manuscript writing: CM-X, JH-Y, LQ-K, XX-Z, LF-W, XJ-C, HL-L. Studies selecting and data analysis: CM-X, JH-Y, LQ-K. Study quality evaluating: CM-X, LF-W, XJ-C, HL-L, QY. Manuscript revising: CM-X, JH-Y, LQ-K, XX-Z, LF-W, XJ-C, HL-L. All authors have read and approved the final manuscript.

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## Tables

Table 1. Univariate and multivariate analysis of predictors for neck lymph node metastasis

Variables	Neck lymph node metastasis		Univariate p	Logistic regression	
	Positive	Negative		p	OR[95% CI]
Age					
≥57	16	74			
≤57	10	51	0.825		
Sex					
Male	20	91			
Female	6	34	0.665		
Smokers					
Yes	18	84			
No	8	41	0.841		
Drinkers					
Yes	11	50			
No	15	75	0.827		
Perineural invasion					
Yes	6	17			
No	20	108	0.221		
Lymphovascular invasion					
Yes	7	12			
No	19	113	0.015	0.022	2.475 [1.233-4.997]
Pathologic tumor grade					
Low	8	67			
Intermediate + high	18	58	0.034	0.110	2.414 [0.894-6.114]
MRI-determined DOI*					
≥7.5mm	12	26			
≤7.5mm	14	99	0.007	0.009	2.978 [1.574-7.332]
Pathologic DOI					
≥5.0mm	13	30			
≤5.0mm	13	95	0.008	<0.001	3.112 [1.812-9.668]
Tumor growth pattern					
Ulcer type	12	60			
Invasive type	5	15			
Exogenous type	9	50	0.599		

\*: DOI: depth of invasion.

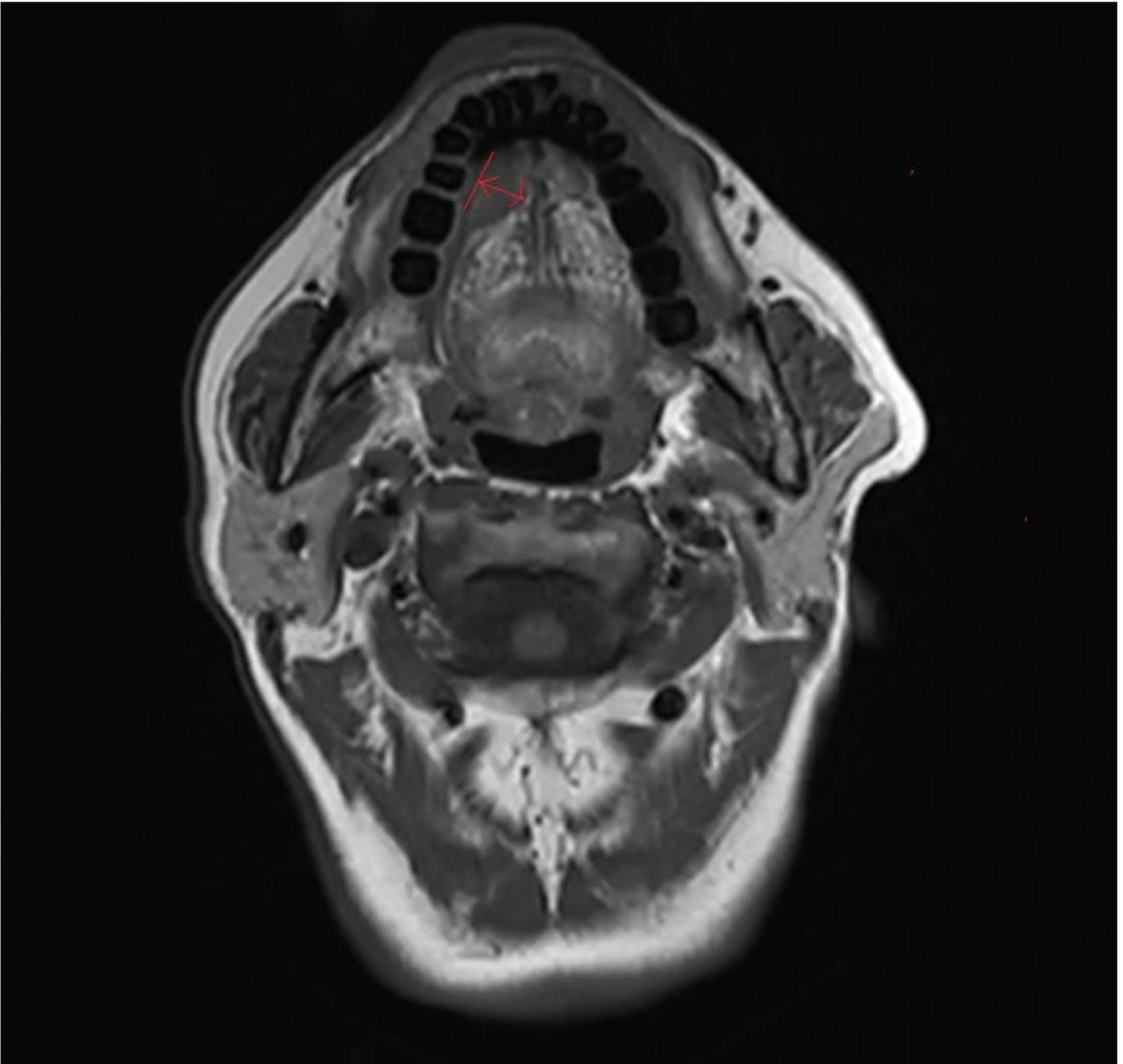
Table 2. Prognostic factors for the locoregional control survival in patients with T1 tumors.

Variables	Univariate		Cox model
	Log-rank test	p	RR[95%CI]
Age	0.634		
Sex	0.187		
Smokers	0.334		
Drinkers	0.227		
Neck lymph node metastasis	0.004	0.035	1.745 [1.152-4.221]
Perineural invasion	0.016	0.114	
Lymphovascular invasion	0.009	0.016	2.007[1.274-5.732]
Pathologic tumor grade	0.095		
MRI-determined DOI	<0.001	<0.001	2.842 [1.449-7.264]
Pathologic DOI	<0.001	<0.001	3.246 [1.679-8.336]
Tumor growth pattern	0.397		
Adjuvant treatment	0.572		

Table 3. Prognostic factors for the disease-specific survival in patients with T1 tumors.

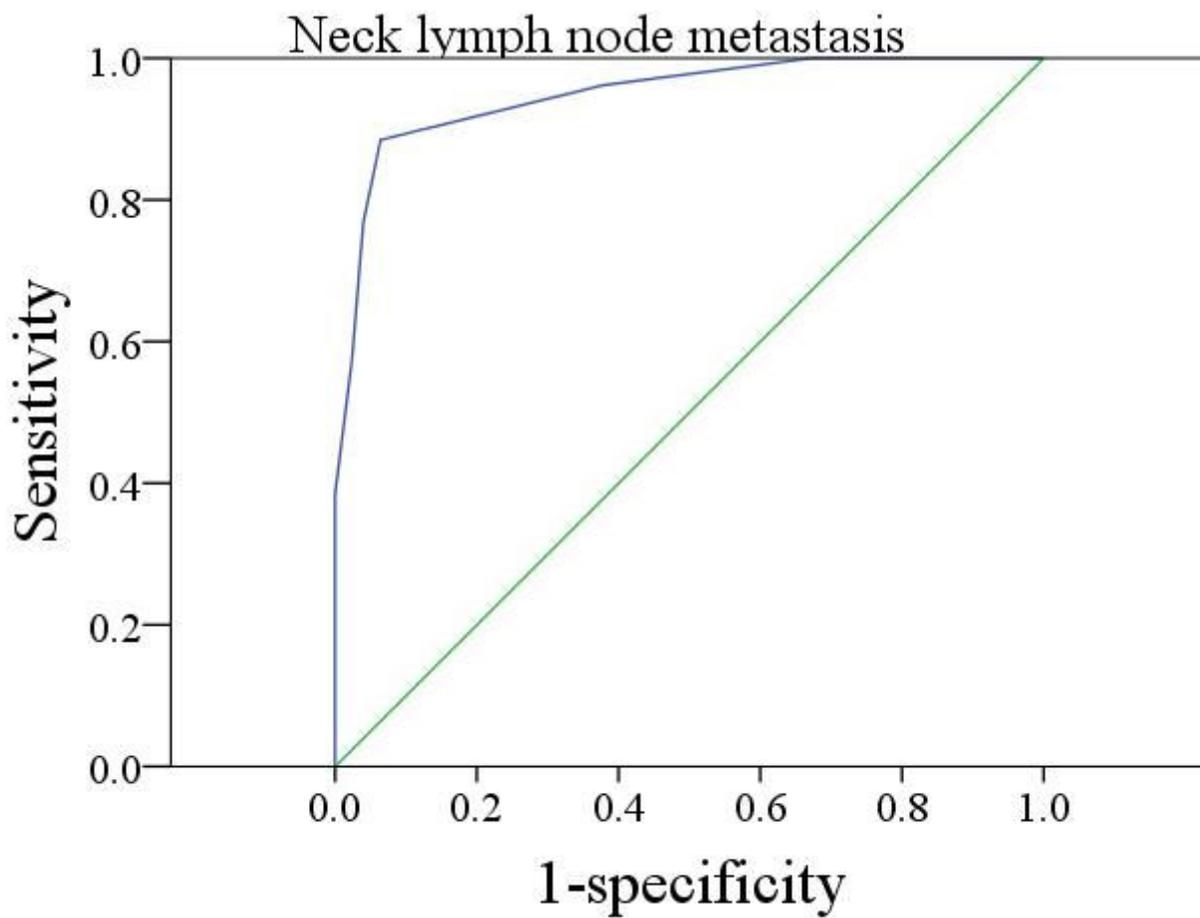
Variables	Univariate		Cox model
	Log-rank test	p	RR[95%CI]
Age	0.241		
Sex	0.387		
Smokers	0.841		
Drinkers	0.458		
Neck lymph node metastasis	0.008	0.005	2.665 [1.442-5.322]
Perineural invasion	0.089		
Lymphovascular invasion	0.110		
Pathologic tumor grade	0.175		
MRI-determined DOI	<0.001	<0.001	2.441 [1.635-5.994]
Pathologic DOI	<0.001	<0.001	3.002 [1.753-6.885]
Tumor growth pattern	0.422		
Adjuvant treatment	0.631		

## Figures



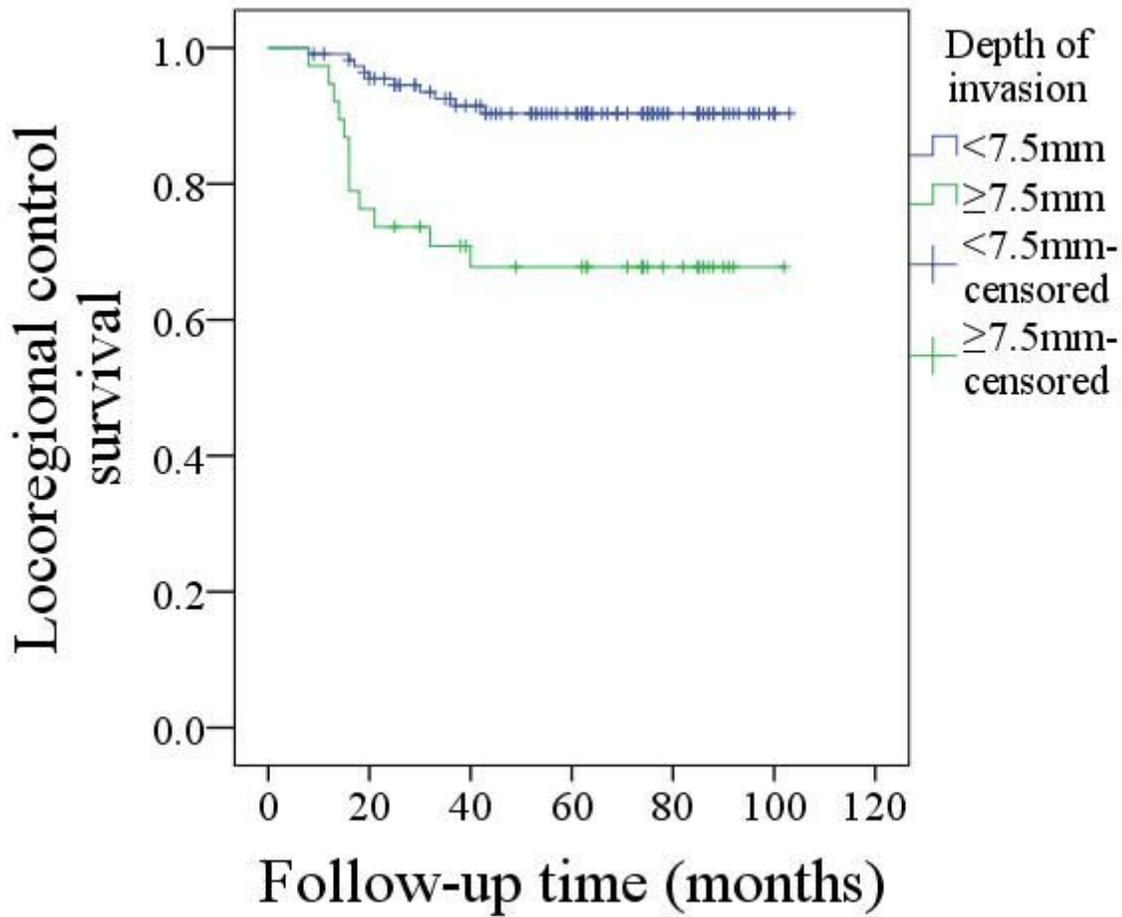
**Figure 1**

Measurement of the MRI-determined depth of invasion based on the adjacent normal mucosal junction to the deepest infiltration point.



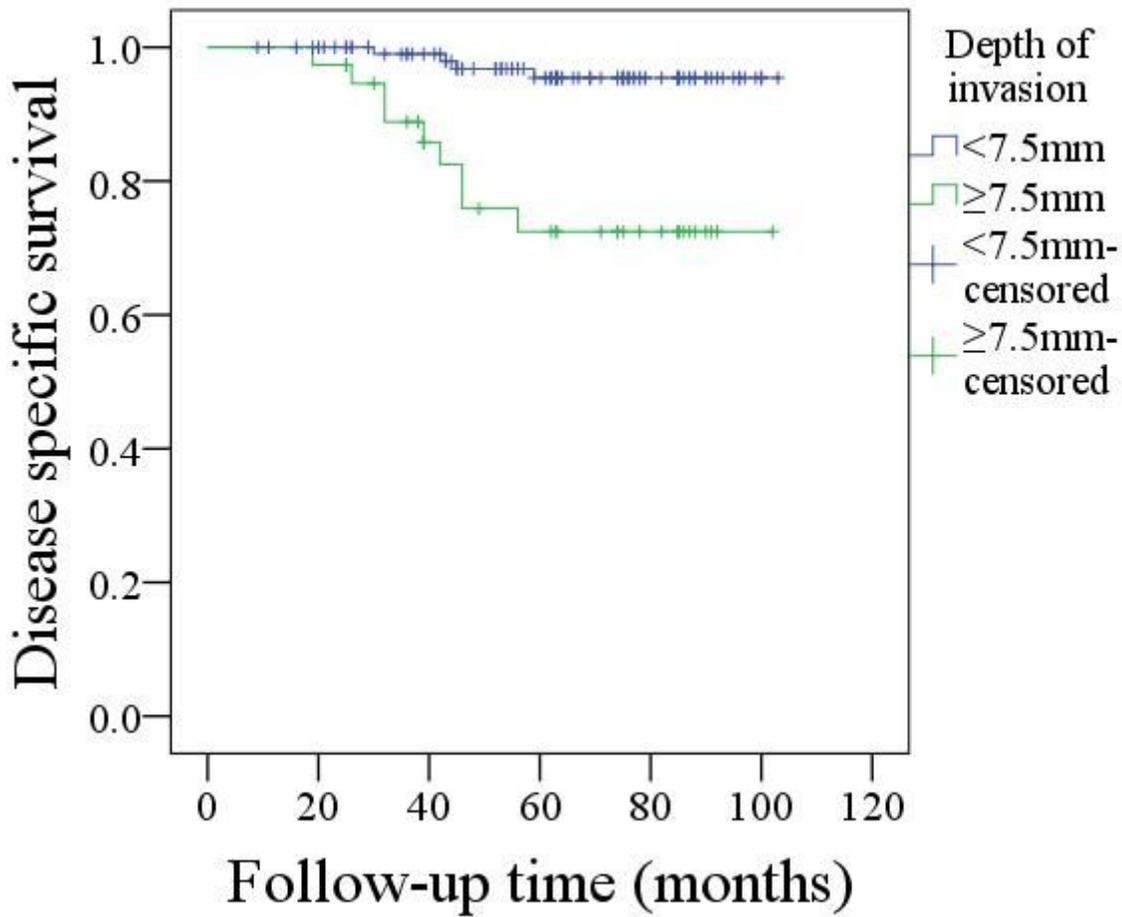
**Figure 2**

ROC analysis of the optimal cutoff value of MRI-determined DOI for predicting neck lymph node metastasis.



**Figure 3**

Comparison of locoregional control survival in patients with different MRI-determined depth of invasion ( $p < 0.001$ ).



**Figure 4**

Comparison of disease specific survival in patients with different MRI-determined depth of invasion ( $p < 0.001$ ).