research article

MRI prognostic factors of tongue cancer: potential predictors of cervical lymph nodes metastases

Mohamed A.F. Mourad, Mahmoud M. Higazi

Department of Radiology, Minia University, Egypt

Radiol Oncol 2019; 53(1): 49-56.

Received 20 October 2018
Accepted 15 January 2019

Correspondence to: Mahmoud M. Higazi, M.D., Lecturer of Radiology, Minia University Egypt. E-mail: mahmoud.higazi@minia.edu.eg

Disclosure: No potential conflicts of interest were disclosed.

Background. This study aimed to evaluate the efficacy of three MR imaging parameters, which are tumour thickness, para-lingual distance and apparent diffusion coefficient (ADC) value for prediction of cervical lymph nodes metastasis in cancer tongue patients.

Patients and methods. Fifty patients with proved cancer tongue by histopathological examination underwent MRI examination. T1 and T2- weighted MRI, diffusion-weighted images and post-contrast T1 fat suppression sequences were used.

Results. The patients were classified according to lymph nodes involvement as seen by MRI into two groups. Significant differences between positive and negative nodes groups were observed regarding tumour thickness and para-lingual distance (p-values = 0.008 and 0.003 respectively). ROC curve analyses revealed cut-off values >13.8 mm and ≤ 3.3 mm for tumour thickness and para-lingual distance respectively for prediction of nodes involvement. No significant differences between patients with and without cervical lymph nodes metastasis were found regarding corresponding ADC value of the tumour (p-value = 0.518).

Conclusions. Para-lingual distance and tumour thickness are factors that could influence pre-operative judgment and prognosis of tongue cancer patients. ADC value of the tumour itself seem not to be a reliable index of cancer progression to regional lymph nodes.

Key words: tongue cancer; tumour thickness; para-lingual distance; apparent diffusion coefficient; cervical lymph nodes metastases

Introduction

Squamous cell carcinoma is the commonest pathology of head and neck cancers and represents at least 90% of oral malignancies.[1] The World Health Organization expects a worldwide rising oral squamous cell carcinomas incidence in the next decades.[2] Most important risk factors including tobacco smoking, alcohol consumption and Human papilloma virus infection (HPV).[1,3] Squamous cell carcinoma of the tongue is one of the most critical issue due to rich vascular and lymphatic supply of the tongue.[4] High morbidity is associated regarding speech, swallowing and mastication with subsequent life upset.[5,6]

Multiple parameters are responsible for patient survival including tumour thickness, para-lingual distance and metastatic cervical lymph nodes that should be well assessed as an informative prognostic parameters for local recurrence and survival.[7-10] Tongue carcinoma is strongly associated with regional lymph nodes metastases. Therefore, it is crucial to improve cervical lymph nodes management as much as possible.[11-13]

Imaging is superior to clinical neck examination for detection of clinically occult subclinical meta-

static lymph nodes. The incidence of occult metastases varies from 20% to 50% and represents a big unsolved issue as a clinically negative patient.[14-18] MRI is considered the widespread imaging modality in assessment of carcinoma of the tongue due to its high soft tissue capability and it can define the true extent, loco-regional involvement and tumour depth. The role of diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) in differentiation of benign from malignant lesions and grading of malignancies is under investigation.[19-22]

In this study, we attempted to detect potential accuracy and cut-off values for MRI tumour thickness and para-lingual distance as well as DWI/ADC values associated with positive cervical lymph nodes spread for better pre-operative evaluation of tongue cancer patients.

Patients and methods

The study included 50 patients who were diagnosed as squamous cell carcinoma of the tongue by histopathological examination. The hospital's ethics committee approved the protocol of the study and all patients enrolled in this study signed the informed consent. The patients underwent MRI examination prior to surgery. MR examinations were performed using a 1.5-T system (Avanto, Siemens, Germany). Head/Neck 20 coil was used. The patient's head was secured using relaxing cushion; ensuring that the shoulders touch the lower part of the coil. The protocol included axial, sagittal and coronal T1-weighted turbo spin echo (TSE), axial and coronal T2-weighted turbo spin echo (TSE) and gadolinium enhanced axial and coronal T1-weighted sequences with fat suppression (FS) as well as diffusion-weighted (DW) sequences. T1-weighted images were done with the following parameters; TR/TE: 550/18 ms; slice thickness/interslice gap: 5/2 mm; mean field of view: 250 mm; slices number: 23; matrix: 320 X 288. T2-weighted turbo spin-echo (TSE) images were done with the following parameters; TR/TE: 4000/41 ms, slice thickness/interslice gap: 5/2 mm; mean field of view: 250 mm; slices number: 23; matrix: 512 X 460. Gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA, Magnevist, Schering, Berlin, Germany) was administered intravenously at a rate of 2 mL/s (total dose, 0.1 mmole/kg of body weight) using a power injector, followed by a 20-mL saline flush.

DWI was done by using the spin echo single-shot by using the spin echo single-shot echo-planar sequence. The parameters were as follows: TR/TE of 3200/70 ms, Slice thickness/inter-slice gap: 5/2 mm, mean field of view of 240mm, slices number: 23, matrix of 192X 192. DWI was done with b-values of 500 and 1000 smm^{-2}. Apparent diffusion coefficient (ADC) maps were then automatically generated. As ADC maps suffer from relatively poor resolution, delineation of the tumour is typically performed on T2 or post-contrast (T1)-weighted images and the region of interest (ROI) is then overlaid on ADC maps.

ROIs were measured from the most representable part of the tumour. The tumour thickness, para-lingual distance and ADC values were measured at coronal MR images separately by the two radiologists shared in the study and inter-observer variability was calculated. The tumour depth and para-lingual distance were measured at post contrast T1 coronal FS. The tumour thickness was defined by the distance from the deepest point of invasion to the tumour surface. At first, a vertical line joining the maximum length between tumour-mucosa junctions was drawn as a reference line. The tumour thickness was determined by summation of two lines drawn perpendicular from the reference line to the point of maximum tumour extension. The para-lingual distance was defined as the distance measured between the para-lingual space and the tumour. The patients in whom tumour invasion extended beyond the midline, the para-lingual distances were expressed as a minus (examples of how the representative lines were drawn are shown on Figures 4 and 5).

Statistical analysis

Descriptive statistics were shown as mean ± SD. The differences between positive and negative nodes metastases groups were detected using two tail Student *t* test. Logistic regression analyses were performed for radiologic predictors of nodes spread. ROC curves were constructed for MRI cut-off values. The inter-observer agreement was assessed using Kappa statistics. The statistical analyses were performed using commercially available software (Medcalc, Version 15 for Windows). P-value (< 0.05) was considered statistically significant.

Results

This study included 50 patients with proved cancer tongue, their mean age was 61 ± 10 years, 34/50

(68%) were males. They all underwent MRI examination for detection of MR tumour thickness and para-lingual distance; including post-contrast study as well as diffusion-weighted imaging with corresponding measurement of ADC values of tumour tissue. According to tumour site, 42/50 (84%) were in oral tongue, while 8/50 (16%) of patients had tongue base tumour. MRI tumour thickness ranged between 5.5 mm and 43.2 mm (16.62 ± 9.45). Para-lingual distances ranged between -15 and 12.4 mm (3.8 ± 5.15). Regression analysis revealed that tumour thickness had a very strong negative association with para-lingual distance (p-value < 0.001 and $R^2 = 0.578$) (Figure 1). Most of the patients had either T1 stage or T2 stage disease. They were 36/50 (72%) patients who had T1 stage and 12/50 (24%) patients who had T2 stage disease. This is while 2/50 patients (4%) had T3 stage disease. The ADC values for tumour tissue of studied population ranged between 0.724 and 1.310 (0.944 ± 0.124). No significant correlation could be detected between T stage of the tumours and their ADC values (p-value = 0.744). The Kappa value for inter-observer agreement was 0.80 indicating substantial to perfect agreement. The patients (either clinically positive or occult for lymph nodes) were classified according to lymph nodes spread as detected by MRI into two groups Table 1 shows absolute values of the three parameters (tumour thickness, para-lingual distance and ADC value) for patients with (N1) and those without (N0) lymph nodes spread.

The 1st group included those patients with positive MRI nodes metastases (N1); they were 28/50 (56%) patients, of which 23/28 (82%) had unilateral lymph nodes metastases; while 5/28 (18%) had bi-

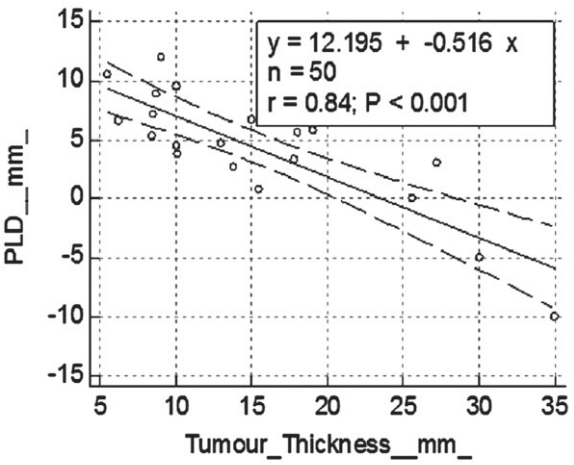

FIGURE 1. Scatter plot showing strong negative correlation between MR tumour thickness and para-lingual distance (p-value < 0.001 and r = 0.84).

TABLE 1. Absolute values for TT, PLD and ADC for (N0) and (N1) LN spread

N0		
TT (mm)	PLD (mm)	ADC
10	9.5	0.899
8.4	5.3	0.937
15	6.7	0.815
8.7	8.9	0.953
10.1	3.8	1.051
5.5	10.5	0.875
6.2	6.6	0.988
9	12	0.836
13	4.7	0.864
8.5	7.2	0.955
9.8	10	0.832
9	7.8	0.968
12.3	6.3	0.843
7.6	9.2	0.915
10.7	4.3	1.31
6.3	10.8	0.864
6.4	6.7	0.978
9.3	12.4	0.834
9.1	7.9	0.869
10	9.5	0.899
8.4	5.3	0.937
8.7	8.9	0.953
N1		
19	5.8	1.18
17.8	3.3	0.928
10	4.5	1.16
15.5	0.8	0.795
13.8	2.7	0.961
18	5.6	0.793
16.9	3.1	0.874
12.3	4.7	1.17
13.7	0.5	0.778
14.8	3.7	0.959
19	5.8	1.18
17.8	3.3	0.928
15	6.7	0.815
13.8	4.4	0.83
35	-10	0.987
27.2	3.1	1.03
30	-5	0.976
25.6	0	0.892
34	-8	0.984
25	7	1.21
23.2	3.2	1.07
29.7	-3	0.938
22.8	0	0.792
21.4	5.8	0.724
27.8	-7	0.852
23.9	0	0.897
42.7	-15	0.893
43.2	-12	1.051

TABLE 2. Summary of descriptive statistics for studied population

	N	N1	N0	P value
Age (mean+/-SD)	61 ± 10	61 ± 11	60 ± 9	0.794
Sex (male, no., %)	34/50 (68%)	20/28 (71%)	14/22 (64%)	_
Tumour Thickness (mean+/-SD)	16.62 ± 9.45	19.8 ± 8.8	9.9 ± 2.6	0.008*
Para-lingual distance (mean+/-SD)	3.8 ± 5.12	0.9 ± 5.5	7.2 ± 2.5	0.003*
ADC (mean+/-SD)	0.944 ± 0.124	0.952 ± 0.112	0.928 ± 0.118	0.518

* = significant p value

lateral lymph nodes on both sides of the neck. MRI tumour thickness of this group ranged between 10 mm and 43.2 mm (19.8 ± 8.8). The para-lingual distance ranged between -15 mm and 7 mm (0.9 ± 5.5). The ADC values ranged between 0.724 and 1.212 (0.952 ± 0.112). The 2nd group included those patients with negative MRI nodes metastases (N0); they were 22/50 (44%) patients. MRI tumour thickness of this group ranged between 6.2 and 15 mm (9.9 ± 2.6). The para-lingual distance ranged between 3.8 mm and 12 mm (7.2 ± 2.5). The ADC values ranged between 0.793 and 1.161 (0.928 ± 0118). Table 2 shows summary of descriptive statistics for the two groups of the study.

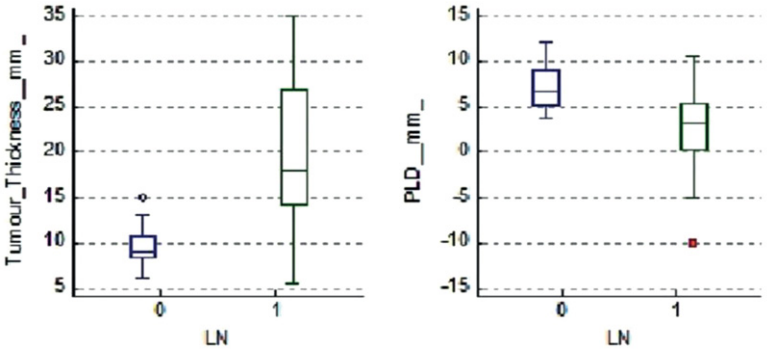

FIGURE 2. Comparison graphs illustrating the significant differences between tumour thickness and para-lingual distance among nodes positive (N1) and negative (N0) patients (p-values 0.008 and 0.003 respectively).

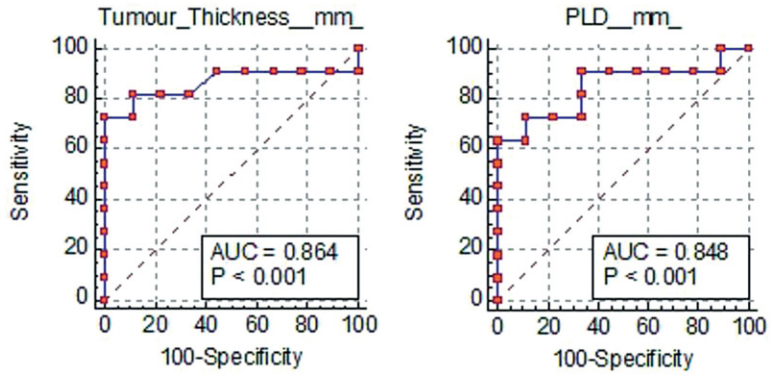

FIGURE 3. Receiver Operator Characteristic (ROC) curve analyses for tumour thickness and para-lingual distance predicting nodes spread (p-values < 0.001 and AUC 0.864 and 0.848 respectively).

Significant differences between the two groups were observed regarding tumour thickness and para-lingual distance (p-values 0.008 and 0.003 respectively) (Figure 2); while ADC values were not significantly different between patients with and without lymph nodes metastases (p-value 0.518). Logistic regression analyses (Table 2) showed that MRI tumour thickness and para-lingual distance were significant strong predictors for positive nodes metastases (p-values < 0.0001, 0.0001 and R^2 0.755, 0.697 respectively). This is while ADC value does not seem to be useful for prediction of lymph nodes metastases (p-value = 0.472). ROC curve analyses (Figure 3) revealed cut-off value > 13.8 mm for tumour thickness for prediction of positive nodes metastases; which achieved 72% sensitivity and 88% specificity (AUC = 0.864, p-value = 0.0001 and 95% confidence interval 0.637 to 0.974). For para-lingual distance, the detected cut-off value for prediction of positive nodes metastases was ≤ 3.3 mm, which resulted in best sensitivity (64%) and specificity (89%) (AUC = 0.848, p-value = 0.0002 and 95% confidence interval 0.619 to 0.967). Representative example for T1N0 patient who showed MRI negative lymph nodes spread is shown at (Figure 4) and another T4N1 patient who had MRI positive lymph nodes spread is shown at (Figure 5).

Discussion

Lymph nodes metastasis in many cancers including head and neck cancers is an important clinically accepted prognostic factor; either reflecting tumour aggressiveness or invasiveness or being an indicator for further tumour dissemination.[23]

TABLE 3. Logistic regression analysis for independent variables predicting LN spread

	P value	R2	Odds Ratio	95% CI
Age	0.926	0.0005	1.004	0.917 to 1.099
Tumour Thickness	<0.0001**	0.755	1.756	1.075 to 2.866
Para-lingual distance	0.0001**	0.697	0.325	0.107 to 0.982
ADC	0.472	0.023	1.003	0.995 to 1.015

** = highly significant p value; CI: confidence Interval

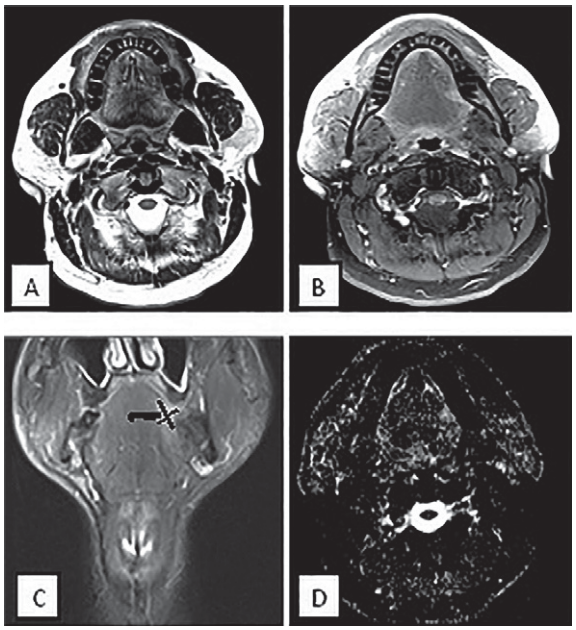

FIGURE 4. MRI of a male patient 65-years-old with small lesion at left hemi-tongue (T1N0) disease. **(A)** Axial T2 **(B)** Axial T1 fat suppression post contrast **(C)** T2 coronal **(D)** Axial DWI. MRI and elective dissected neck revealed no positive cervical lymph nodes spread. The vertical black line was drawn as a reference line connecting maximum tumour-mucosa junctions. Two horizontal lines were drawn perpendicular to the reference line. Tumour thickness is the sum of both of these horizontal lines and was determined as 5.5 mm. The thick black line between the tumour and the para-lingual space represented the para-lingual distance = 10.5 mm.

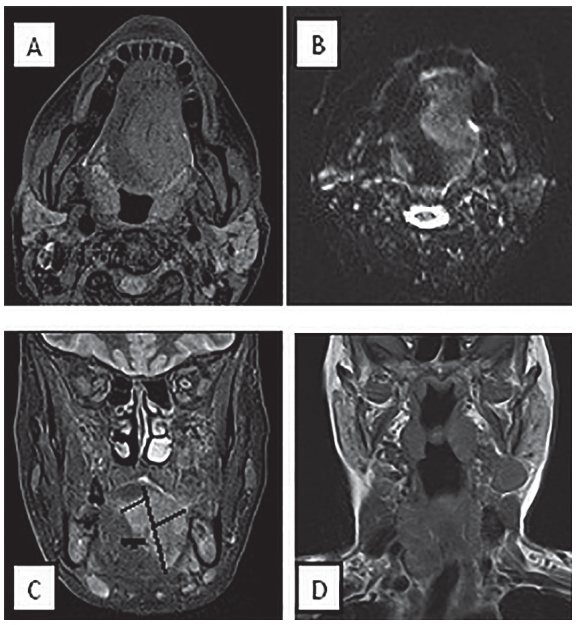

FIGURE 5. MRI of a 75-years-old female with sizable tongue mass crossing the midline (T4N1 disease). **(A)** Axial T1 post contrast fat suppression **(B)** Axial DWI **(C)** Coronal T1 post contrast fat suppression **(D)** Coronal T1 post contrast shows metastatic cervical lymph nodes. Tumour thickness is the sum of the two horizontal black lines drawn perpendicular to the vertical black line connecting maximum tumour junction distance and was determined as 30 mm. The thick black line representing para-lingual distance between the tumour and the para-lingual space was determined as – 10 as the tumour margin extends beyond the midline by 10 mm

Therefore; an accurate preoperative assessment of lymph nodes spread is essential to provide an appropriate management strategy for head and neck cancer patients.[8] The lymphatic system serves as a primary escape route for cancer. Lymphatic capillaries have a thin discontinuous basement membrane, and contain endothelial gaps that can be invaded by cancer cells. In addition, tumour cells secrete factors that stimulate lymphangiogenesis.[24] Cancer cells commonly metastasize through these lymphatic vessels to regional lymph nodes. The presence of metastatic cells in the sentinel lymph nodes is a prognostic indicator for many types of cancer, and the degree of dissemination determines the therapeutic course of action.[24]

In this study, we found that both tumour thickness and para-lingual distance which measured at pre-treatment MRI were significantly different between patients who had positive versus negative cervical lymph nodes spread. Tumour thickness and para-lingual distance were important predictors for cervical lymph nodes spread in tongue

cancer patients in our study. This may be a logic relation which can be easily explained by that with deeper local invasion, tumour cells may come close to deep blood vessels and lymphatics which would carry tumour emboli to regional lymph nodes.[25] This relation is supported by that therapeutic strategies which target both tumour -associated blood and lymphatic vessels can lead to a decrease in tumour size and decrease incidence of local/distant spread.[24]

There are several studies which tested the reliability of MRI in measuring tongue tumour thickness, and correlated it well with histologic tumour thickness.[26-28] Spiro *et al.*, postulated that disease-related death is apparently unusual when oral tumours are thin, regardless of tumour stage, and that tumour thickness rather than stage may have the best correlation with treatment failure and survival.[29] However; tongue cancer may vary in shape and growth pattern. Therefore, depth of invasion (represented by para-lingual distance), not merely tumour thickness, is another important prognostic factor.[30-32]

Recent research is directed at establishing important prognostic pre-operative cut-off values for cancer tongue. Some investigators have attempted to define a cut-off point for oral cavity cancer thickness that correlates well with positive lymph nodes spread.[30,33] Yuen *et al.* have demonstrated 44% incidence of cervical lymph nodes metastases for tumours having a thickness between 3 mm and 9 mm.[34] Jung *et al.* recommended a cut-off value of 11 mm on contrast-enhanced T1-weighted images and showed a significant correlation with nodes metastasis.[35] In this study; tumour thickness value > 13.8 mm and para-lingual distance value ≤ 3.3 mm were detected as best cut-off values for prediction of MRI detectable positive nodes spread. According to Okura *et al.*, preoperative decision to perform elective neck dissection can be based on tumour thickness of > 9.7 mm and para-lingual distance of < 5.2 mm.[18] This should be kept in mind when planning for prophylactic neck dissection especially in clinically negative nodes.[36] These results are in coincidence with AJCC (8th edition) recommendations of reporting tumour thickness during oral cancer staging.[37]

Multiple pulse sequences had been used in previous works to detect small tongue cancers and accurately identify tumour margins, including T2WI, STIR and T1-weighted fat-suppressed contrast-enhanced sequences. Lam *et al.* reported that particularly contrast-enhanced T1-weighted MRI, provides satisfactory accurate correlation between MRI tumour thickness and histologic tumour thickness in oral tongue cancer.[28] Background Diffusion-weighted imaging obtained with magnetic resonance (DW-MRI) is a non-invasive imaging tool potentially able to provide information about micro-structure tumour characteristics.[38,39] The inclusion of DWI/ADC values might be helpful for differentiation between true tumour margin and oedema; and also for distinction between benign and malignant head and neck tumours.[20,21,40] Multiple studies reported high diagnostic accuracy of DWI for differentiation of malignant from benign status of metastatic cervical lymph nodes.[21,40,41]

In this study ADC value does not seem to be an important predictor of metastatic cervical lymph nodes spread. We did not find any significant differences between positive and negative nodes groups regarding tumour ADC values. Curvo-Semedo *et al.* found that pre-treatment ADC values were significantly lower for tumour s with higher T stages and extra-nodal tumour deposits.[42] This was explained by the fact that ADC values are derived from the diffusive movement of water molecules, which is often influenced by cell density, and other histological components. The lower ADC values of malignant tumours can be attributed to the histopathological characteristics of such tumours *i.e.* presence of a more abundant macromolecular protein contents, an enlarged nuclear: cytoplasmic ratio, hyper-chromatism and hypercellularity which are associated with poorly differentiated SCC with a resultant decrease of ADC values.[43] Thus, ADC values might reflect the aggressiveness of a particular tumour tissue. The earlier mentioned studies demonstrated the potential capability of ADC value for characterization of head and neck cancers, but they suffer from the limited number of studied patients, as well as a certain degree of inevitable overlap between different tumour types. Therefore, care should be taken when translating the results of these published studies in daily routine clinical practice. Multi-centeric studies in a large cohort of patients with identical imaging protocols are required to substantiate these preliminary results.

Whether ADC values of tumours can be helpful for predicting tumour aggressiveness is a matter of debate that may require further justification. Sun *et al.* revealed no statistically significant correlation between ADC value and tumour differentiation grade upon histological examination.[43] Also, our results are supported by Bonello *et al.* as they did not observe any statistically significant correlation between ADC values and clinical-histological

characteristics of SCCA of the oral cavity and oropharynx.[44] The poorly differentiated squamous cell carcinoma (SCC) might have a high degree of small foci of tissue necrosis than well-differentiated SCC, which was confirmed histopathologically. These areas of tumour necrosis will ultimately result in increased membrane permeability through breakdown of cell membrane, with consequently free diffusion.[43] In addition; higher proportion of tumour stroma is acting as stimulator of cancer growth. Tumour associated fibroblasts (TAFs) are the largest stromal cellular components of the tumour microenvironment in head and neck squamous cell carcinomas. Tumour associated fibroblasts enhance cancer proliferation, invasion, and metastasis.[45]

The preoperative decision of the extent of neck dissection based on ADC value measurements alone might be useless in daily clinical practice. Moreover, it may offer false impression to clinicians about the chance of lymph nodes spread. This is unlike the information derived from simple measurements of tumour dimensions and depth of the primary tumour, which can give more reliable data to take an appropriate management plan decisions.

The limitations of our study include the relative small number of cases pertaining to each group and errors caused by manual measurement of tumour thickness and para-lingual distances. Additionally, artifacts due to tongue motion or dental fillings were a limiting factor and the patients had to be well sedated and in most comfortable position during examination. The inevitable individual difference of manual ADC measurements, ROI size and shape is another limitation, which may result in different outcomes.

Conclusions

Tumour thickness and para-lingual distance are important prognostic factors that motivate the search for metastatic cervical lymph nodes to better tailor pre-operative judgment and management plan of cancer tongue patients. ADC value of the tumour itself is not a reliable index that could be useful in daily clinical practice to pinpoint to the stage of cancer progression. Further long term large scale studies are recommended for assessment of relation between tumour ADC value and anticipated nodes spread in cancers as well as influence upon survival rate.

References

1. Funk GF, Karnell LH, Robinson RA, Zhen WK, Trask DK, Hoffman HT. Presentation, treatment, and outcome of oral cavity cancer: a National Cancer Data Base report. *Head Neck* 2002; **24:** 165-80.
2. Lubek JE, Clayman L. An update on squamous carcinoma of the oral cavity, oropharynx, and maxillary sinus. *Oral Maxillofac Surg Clin North Am* 2012; **24:** 307-16, x. doi: 10.1016/j.coms.2012.01.003
3. Syrjanen S. Human papillomavirus infections and oral tumors. *Med Microbiol Immunol* 2003; **192:** 123-8. doi: 10.1007/s00430-002-0173-7
4. Tshering Vogel DW, Zbaeren P, Thoeny HC. Cancer of the oral cavity and oropharynx. *Cancer Imaging* 2010; **10:** 62-72. doi: 10.1102/1470-7330.2010.0008
5. Stone M, Davis EP, Douglas AS, Aiver MN, Gullapalli R, Levine WS, et al. Modeling tongue surface contours from Cine-MRI images. *J Speech Lang Hear Res* 2001; **44:** 1026-40.
6. Wilhelms-Tricarico R. Physiological modeling of speech production: methods for modeling soft-tissue articulators. *J Acoust Soc Am* 1995; **97:** 3085-98.
7. Kane SV, Gupta M, Kakade AC, D'Cruz A. Depth of invasion is the most significant histological predictor of subclinical cervical lymph node metastasis in early squamous carcinomas of the oral cavity. *Eur J Surg Oncol* 2006; **32:** 795-803. doi: 10.1016/j.ejso.2006.05.004
8. Clark JR, Naranjo N, Franklin JH, Almeida J de, Gullane PJ. Established prognostic variables in NO oral carcinoma. *Otolaryngol Neck Surg* 2006; **135:** 748-53. doi: 10.1016/j.otohns.2006.05.751
9. Yamazaki H, Inoue T, Yoshida K, Tanaka E, Yoshioka Y, Nakamura H, et al. Lymph node metastasis of early oral tongue cancer after interstitial radiotherapy. *Int J Radiat Oncol Biol Phys* 2004; **58:** 139-46. doi: 10.1016/S0360-3016(03)01459-7
10. Mohit-Tabatabai MA, Sobel HJ, Rush BF, Mashberg A. Relation of thickness of floor of mouth stage I and II cancers to regional metastasis. *Am J Surg* 1986; **152:** 351-3.
11. Alsaffar HA, Goldstein DP, King E V, de Almeida JR, Brown DH, Gilbert RW, et al. Correlation between clinical and MRI assessment of depth of invasion in oral tongue squamous cell carcinoma. *J Otolaryngol Head Neck Surg* 2016; **45:** 61. doi: 10.1186/s40463-016-0172-0
12. O-charoenrat P, Pillai G, Patel S, Fisher C, Archer D, Eccles S, et al. Tumour thickness predicts cervical nodal metastases and survival in early oral tongue cancer. *Oral Oncol* 2003; **39:** 386-90. doi: 10.1016/S1368-8375(02)00142-2
13. Huang SH, Hwang D, Lockwood G, Goldstein DP, O'Sullivan B. Predictive value of tumor thickness for cervical lymph-node involvement in squamous cell carcinoma of the oral cavity. *Cancer* 2009; **115:** 1489-97. doi: 10.1002/cncr.24161
14. Franceschi D, Gupta R, Spiro RH, Shah JP. Improved survival in the treatment of squamous carcinoma of the oral tongue. *Am J Surg* 1993; **166:** 360-5. doi: 10.1016/S0002-9610(05)80333-2
15. Byers RM, El-Naggar AK, Lee YY, Rao B, Fornage B, Terry NH, et al. Can we detect or predict the presence of occult nodal metastases in patients with squamous carcinoma of the oral tongue? *Head Neck* 1998; **20:** 138-44.
16. Ferlito A, Rinaldo A, Silver CE, Gourin CG, Shah JP, Clayman GL, et al. Elective and therapeutic selective neck dissection. *Oral Oncol* 2006; **42:** 13-24. doi: 10.1016/j.oraloncology.2005.03.009
17. Takes RP, Righi P, Meeuwis CA, Manni JJ, Knegt P, Marres HA, et al. The value of ultrasound with ultrasound-guided fine-needle aspiration biopsy compared to computed tomography in the detection of regional metastases in the clinically negative neck. *Int J Radiat Oncol Biol Phys* 1998; **40:** 1027-32. doi: 10.1016/S0360-3016(97)00953-X
18. Okura M, Iida S, Aikawa T, Adachi T, Yoshimura N, Yamada T, et al. Tumor thickness and paralingual distance of coronal MR imaging predicts cervical node metastases in oral tongue carcinoma. *Am J Neuroradiol* 2008; **29:** 45-50. doi: 10.3174/ajnr.A0749
19. Sumi M, Sakihama N, Sumi T, Morikawa M, Uetani M, Kabasawa H, et al. Discrimination of metastatic cervical lymph nodes with diffusion-weighted MR imaging in patients with head and neck cancer. *AJNR Am J Neuroradiol* 2003; **24:** 1627-34.

20. Srinivasan A, Dvorak R, Perni K, Rohrer S, Mukherji SK. Differentiation of benign and malignant pathology in the head and neck using 3T apparent diffusion coefficient values: early experience. *Am J Neuroradiol* 2008; **29:** 40-4. doi: 10.3174/ajnr.A0743

21. Vandecaveye V, De Keyzer F, Vander Poorten V, Dirix P, Verbeken E, Nuyts S, et al. Head and neck squamous cell carcinoma: value of diffusion-weighted MR imaging for nodal staging. *Radiology* 2009; **251:** 134-46. doi: 10.1148/radiol.2511080128

22. Park JO, Jung SL, Joo YH, Jung CK, Cho KJ, Kim MS. Diagnostic accuracy of magnetic resonance imaging (MRI) in the assessment of tumor invasion depth in oral/oropharyngeal cancer. *Oral Oncol* 2011; **47:** 381-6. doi: 10.1016/j.oraloncology.2011.03.012

23. Cho JK, Hyun SH, Choi N, Kim MJ, Padera TP, Choi JY, et al. Significance of lymph node metastasis in cancer dissemination of head and neck cancer. *Transl Oncol* 2015; **8:** 119-25. doi: 10.1016/j.tranon.2015.03.001

24. Zwaans BMM, Bielenberg DR. Potential therapeutic strategies for lymphatic metastasis. *Microvasc Res* 2007; **74:** 145-58. doi: 10.1016/j.mvr.2007.08.006

25. Chen SL, Iddings DM, Scheri RP, Bilchik AJ. Lymphatic mapping and sentinel node analysis: current concepts and applications. *CA Cancer J Clin* 2006; **56:** 292-309; quiz 316-7.

26. Goel V, Parihar PS, Parihar A, Goel AK, Waghwani K, Gupta R, et al. Accuracy of MRI in prediction of tumour thickness and nodal stage in oral tongue and gingivobuccal cancer with clinical correlation and staging. *J Clin Diagnostic Res* 2016; **10:** TC01-5. doi: 10.7860/JCDR/2016/17411.7905

27. Bashir U, Manzoor MU, Majeed Y, Khan RU, Hassan U, Murtaza A, et al. Reliability of MRI in measuring tongue tumour thickness: a 1.5T study. *J Ayub Med Coll Abbottabad* 2011; **23:** 101-4.

28. Lam P, Au-Yeung KM, Cheng PW, Wei WI, Yuen AP, Trendell-Smith N, et al. Correlating MRI and histologic tumor thickness in the assessment of oral tongue cancer. *Am J Roentgenol* 2004; **182:** 803-8. doi: 10.2214/ajr.182.3.1820803

29. Spiro RH, Huvos AG, Wong GY, Spiro JD, Gnecco CA, Strong EW. Predictive value of tumor thickness in squamous carcinoma confined to the tongue and floor of the mouth. *Am J Surg* 1986; **152:** 345-50.

30. Hegde P, Roy S, Shetty T, Prasad BR, Shetty U. Tumor infiltration depth as a prognostic parameter for nodal metastasis in oral squamous cell carcinoma. *Int J Appl basic Med Res* 2017; **7:** 252-7. doi: 10.4103/ijabmr.IJABMR_66_17

31. Almangush A, Bello IO, Keski-Säntti H, Mäkinen LK, Kauppila JH, Pukkila M, et al. Depth of invasion, tumor budding, and worst pattern of invasion: prognostic indicators in early-stage oral tongue cancer. *Head Neck* 2014; **36:** 811-8. doi: 10.1002/hed.23380

32. Pentenero M, Gandolfo S, Carrozzo M. Importance of tumor thickness and depth of invasion in nodal involvement and prognosis of oral squamous cell carcinoma: a review of the literature. *Head Neck* 2005; **27:** 1080-91. doi: 10.1002/hed.20275

33. Mücke T, Kanatas A, Ritschl LM, Koerdt S, Tannapfel A, Wolff KD, et al. Tumor thickness and risk of lymph node metastasis in patients with squamous cell carcinoma of the tongue. *Oral Oncol* 2016; **53:** 80-4. doi: 10.1016/j.oraloncology.2015.11.010

34. Yuen AP, Ho CM, Chow TL, Tang LC, Cheung WY, Ng RW, et al. Prospective randomized study of selective neck dissection versus observation for N0 neck of early tongue carcinoma. *Head Neck* 2009; **31:** 765-72. doi: 10.1002/hed.21033

35. Jung J, Cho NH, Kim J, Choi EC, Lee SY, Byeon HK, et al. Significant invasion depth of early oral tongue cancer originated from the lateral border to predict regional metastases and prognosis. *Int J Oral Maxillofac Surg* 2009; **38:** 653-60. doi: 10.1016/j.ijom.2009.01.004

36. Jarungroongruangchai W, Charoenpitakchai M, Silpeeyodom T, Pruksapong C, Burusapat C. Size of cervical lymph node and metastasis in squamous cell carcinoma of the oral tongue and floor of mouth. *J Med Assoc Thai* 2014; **97 (Suppl 2):** S101-6.

37. Huang SH, O'Sullivan B. Overview of the 8th edition TNM classification for head and neck cancer. *Curr Treat Options Oncol* 2017; **18:** 40. doi: 10.1007/s11864-017-0484-y

38. Charles-Edwards EM, deSouza NM. Diffusion-weighted magnetic resonance imaging and its application to cancer. *Cancer Imaging* 2006; **6:** 135-43. doi: 10.1102/1470-7330.2006.0021

39. Chilla GS, Tan CH, Xu C, Poh CL. Diffusion weighted magnetic resonance imaging and its recent trend-a survey. *Quant Imaging Med Surg* 2015; **5:** 407-22. doi: 10.3978/j.issn.2223-4292.2015.03.01

40. Vandecaveye V, De Keyzer F, Hermans R. Diffusion-weighted magnetic resonance imaging in neck lymph adenopathy. *Cancer Imaging* 2008; **8:** 173-80. doi: 10.1102/1470-7330.2008.0025

41. Holzapfel K, Duetsch S, Fauser C, Eiber M, Rummeny EJ, Gaa J. Value of diffusion-weighted MR imaging in the differentiation between benign and malignant cervical lymph nodes. *Eur J Radiol* 2009; **72:** 381-7. doi: 10.1016/j.ejrad.2008.09.034

42. Curvo-Semedo L, Lambregts DMJ, Maas M, Beets GL, Caseiro-Alves F, Beets-Tan RGH. Diffusion-weighted MRI in rectal cancer: Apparent diffusion coefficient as a potential noninvasive marker of tumor aggressiveness. *J Magn Reson Imaging* 2012; **35:** 1365-71. doi: 10.1002/jmri.23589

43. Sun Y, Tong T, Cai S, Bi R, Xin C, Gu Y. Apparent diffusion coefficient (ADC) value: a potential imaging biomarker that reflects the biological features of rectal cancer. *PLoS One* 2014; **9:** e109371. doi: 10.1371/journal.pone.0109371

44. Bonello L, Preda L, Conte G, Giannitto C, Raimondi S, Ansarin M, et al. Squamous cell carcinoma of the oral cavity and oropharynx: what does the apparent diffusion coefficient tell us about its histology? *Acta Radiol* 2016; **57:** 1344-51. doi: 10.1177/0284185115587734

45. Wheeler SE, Shi H, Lin F, Bednash J, Thorne S, Watkins S, et al. Enhancement of head and neck squamous cell carcinoma proliferation, invasion, and metastasis by tumor-associated fibroblasts in preclinical models. *Head Neck* 2014; **36:** 385-92. doi: 10.1002/hed.23312