



# Diffusion-weighted Magnetic Resonance Imaging for Predicting Response to Chemoradiation Therapy for Head and Neck Squamous Cell Carcinoma: A Systematic Review

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**Objective:** To systematically review the evaluation of the diagnostic accuracy of pre-treatment apparent diffusion coefficient (ADC) and change in ADC during the intra- or post-treatment period, for the prediction of locoregional failure in patients with head and neck squamous cell carcinoma (HNSCC).

**Materials and Methods:** Ovid-MEDLINE and Embase databases were searched up to September 8, 2018, for studies on the use of diffusion-weighted magnetic resonance imaging for the prediction of locoregional treatment response in patients with HNSCC treated with chemoradiation or radiation therapy. Risk of bias was assessed by using the Quality Assessment Tool for Diagnostic Accuracy Studies-2.

**Results:** Twelve studies were included in the systematic review, and diagnostic accuracy assessment was performed using seven studies. High pre-treatment ADC showed inconsistent results with the tendency for locoregional failure, whereas all studies evaluating changes in ADC showed consistent results of a lower rise in ADC in patients with locoregional failure compared to those with locoregional control. The sensitivities and specificities of pre-treatment ADC and change in ADC for predicting locoregional failure were relatively high (range: 50–100% and 79–96%, 75–100% and 69–95%, respectively). Meta-analytic pooling was not performed due to the apparent heterogeneity in these values.

**Conclusion:** High pre-treatment ADC and low rise in early intra-treatment or post-treatment ADC with chemoradiation, could be indicators of locoregional failure in patients with HNSCC. However, as the studies are few, heterogeneous, and at high risk for bias, the sensitivity and specificity of these parameters for predicting the treatment response are yet to be determined.

**Keywords:** *Head and neck; Squamous cell carcinoma; Cancer; DWI; Diffusion-weighted imaging; Apparent diffusion coefficient; Prediction; Treatment response; Response assessment; Systematic review; Meta-analysis*

## INTRODUCTION

Patients with advanced-stage head and neck squamous

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cell carcinoma (HNSCC) are mainly treated with the non-surgical methods of concurrent chemoradiation therapy (CCRT) or radical radiotherapy to preserve organ function and maintain the quality of life (1, 2). Despite these rigorous treatment methods, treatment still fails at local or nodal sites in the head and neck in approximately 25–30% of patients (3-8). A reliable indicator for pre-treatment diagnosis of resistant HNSCC in patients could allow the CCRT regimens to be modified, or indicate the need for a switch to alternative strategies, improving their chances of success, and sparing the patients from ineffective treatment burdened by unnecessary toxicity (9). In addition, intra-treatment scanning for the adaptation of radiotherapy fields to the changing size of the tumor is already under

evaluation, providing an opportunity to monitor early treatment response and adjust CCRT regimes accordingly (1, 2, 10, 11). However, differentiation of residual cancer from post-treatment change using conventional magnetic resonance imaging (MRI), computed tomography (CT), 18-fluorodeoxyglucose positron emission tomography-CT ( $^{18}\text{F}$ -FDG PET/CT) in the early post-treatment period is a dilemma. The morphological criteria of CT and MRI with regard to volume regression (12-16), change in signal intensity (17, 18), and nodal density (19, 20) have shown heterogeneous results in the prediction of treatment response. The image results from  $^{18}\text{F}$ -FDG PET/CT are also often suboptimal due to low spatial resolution and presence of treatment-induced inflammation during the first four months post CCRT that may be misleading (21). Endoscopy of primary sites could be hampered by radiation-induced mucositis. Biopsy of primary and nodal sites could be affected by sampling errors and may initiate superimposed infection, fail to heal, and cause worsening of complaints (22).

Diffusion-weighted imaging (DWI) is a functional MRI technique allowing the quantification of the diffusion of water molecules in a tumor by measuring the apparent diffusion coefficient (ADC). Recently, researchers have focused on DWI for predicting treatment response in patients with HNSCC, and it has been demonstrated that tumors with high ADC values are less likely to respond to chemoradiation (23-32). This is probably because a high ADC value may reflect the presence of micronecrosis, tumor hypoxia, high stromal content, and low cellularity (lower proliferation), which consequently increase the resistance to CCRT. In addition, the diagnostic accuracy of change in ADC values between the pre-treatment and early intra-treatment or post-treatment periods has been investigated for the prediction of treatment response, under the consideration that treatment with CCRT leads to cell death and reduction of restrictive barriers to diffusion, and therefore a consequent increase in the mean ADC value (9, 28, 30, 33, 34). However, several conflicting results have been reported (9, 25, 34-39), and previous studies have been limited by small numbers of patients and overlapping patient data (22, 29-32, 34, 40). To the best of our knowledge, no systematic review has assessed the role of DWI in predicting locoregional failure according to pre-treatment ADC and change in ADC during early intra-treatment or post-treatment in patients with HNSCC. Therefore, we performed this systematic review to evaluate the sensitivity and specificity of pre-treatment ADC and change in ADC during

the early intra-treatment or post-treatment period, for the prediction of the locoregional response to definitive CCRT or radiation therapy in patients with HNSCC.

## MATERIALS AND METHODS

### Literature Search Strategy

A computerized search of the Ovid-MEDLINE and Embase databases was performed to identify relevant original articles on the use of DWI for the prediction of locoregional treatment response in patients with HNSCC treated with definitive CCRT or radiation therapy, up until September 8, 2018. The following search terms were used: [(“head and neck”) OR (oropharyngeal) OR (tongue) OR (oral cavity) OR (oropharynx) OR (hypopharyngeal) OR (hypopharynx) OR (larynx) OR (laryngeal) OR (pharynx) OR (pharyngeal)] AND [(carcinoma) OR (carcinomas) OR (cancer) OR (cancers)] AND [(chemoradiation) OR (chemoradiotherapy) OR (radiotherapy) OR (radiation therapy)] AND [(“diffusion weighted”) OR (“diffusion-weighted”) OR (dw-mri) OR (DWI) OR (“apparent diffusion coefficient”) OR (ADC)]. Only studies published in English were included. The bibliographies of the selected articles were screened to identify other relevant articles.

### Inclusion Criteria

Studies investigating the use of DWI for the prediction of locoregional treatment response in HNSCC were eligible for inclusion.

Studies or subsets of studies satisfying all of the following criteria were included:

- 1) Population: patients with histologically proven HNSCC who underwent definitive CCRT or radiation therapy.
- 2) Index test: imaging with MRI including DWI with provision of pre-treatment ADC value or change in the pre-treatment and early intra-treatment or post-treatment ADC values.
- 3) Reference standard: the reference standards of the treatment outcome as determined by histologic confirmation or clinical/imaging follow-up, or a combination of these.
- 4) Outcomes: results of locoregional failure after definitive CCRT or radiation therapy, reported in sufficient detail.
- 5) Study design: all observational studies (retrospective or prospective).

### Exclusion Criteria

The exclusion criteria were as follows: 1) case reports, review articles, editorials, letters, comments, and conference proceedings; 2) studies with insufficient data on the locoregional failure and locoregional control; 3) studies that did not provide ADC values; 4) studies that monitored the intra-treatment response during CCRT; and 5) studies with overlapping patients and data. Two reviewers independently selected appropriate study reports using a standardized form.

### Data Extraction

One reviewer extracted data from the studies with the second reviewer double-checking the accuracy of the extracted data and resolving any uncertainty through discussion. The following data were extracted from each of the selected studies onto standardized data forms:

- 1) Study characteristics: authors, year of publication, hospital or medical school, years of patient recruitment, sample size, and study design.
- 2) Demographic and clinical characteristics of patients: mean age, nodule size, and patient reference standards.
- 3) Imaging characteristics: timing of imaging, machine manufacturer and model, magnetic field strength, sequence, slice thickness, gap, and total acquisition time for DWI.
- 4) Interpretation: number of reviewers, experience, presence of consensus data.
- 5) True positives and negatives and false positives and negatives for the prediction of treatment response according to ADC value. In cases of incomplete 2 x 2 tables, the corresponding author was contacted, and data required to generate 2 x 2 tables was requested.

### Quality Assessment

The methodological quality of the included studies was assessed independently by two reviewers using tailored questionnaires devised according to the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) criteria (41). Disagreements were very minor and were resolved by consensus.

### Data Analysis

For the diagnostic accuracy assessment, 2 x 2 data were summarized in forest plots of sensitivity and specificity for each study. Pooling was not performed because of the relatively small number of studies, relatively high risk of bias, and inherent heterogeneity based on varying study

designs among the included studies. The presence of a threshold effect was visually assessed using coupled forest plots of sensitivity and specificity. The Spearman correlation coefficient between the sensitivity and false-positive rate was obtained; a value > 0.6 was deemed a considerable threshold effect (42).

## RESULTS

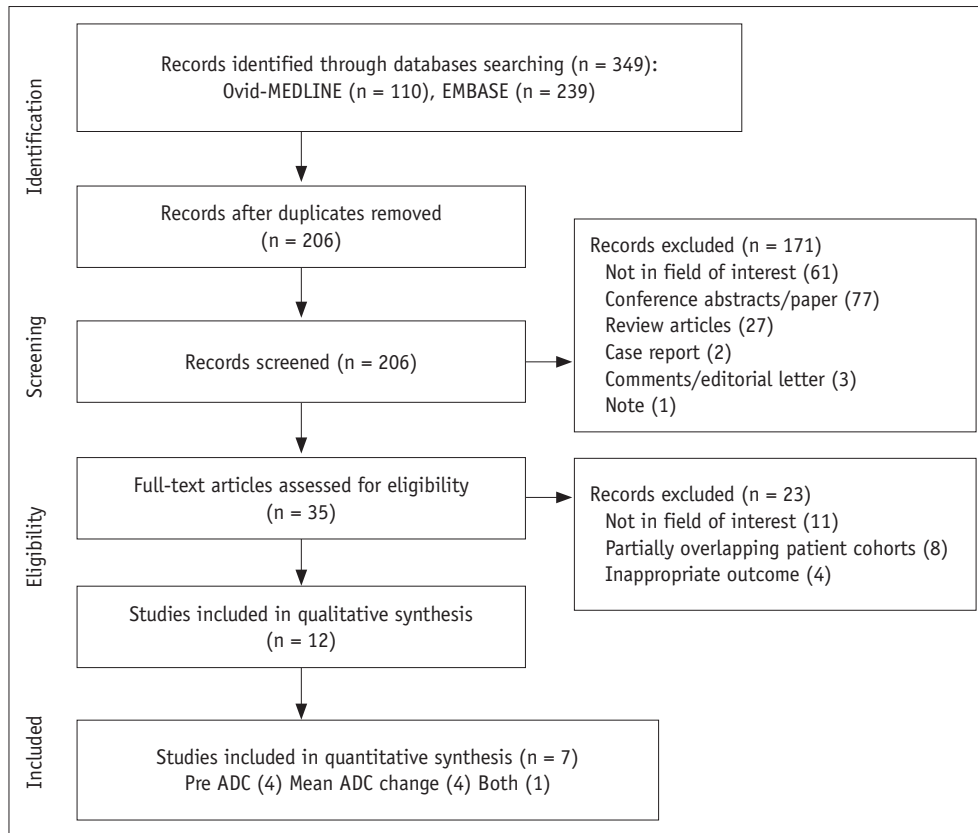
### Literature Search

The study selection process is illustrated in Figure 1. Twelve studies were included in the systematic review and seven of these presented data that could be extracted to a 2 x 2 table format to calculate sensitivity and specificity. The seven studies included four investigating the diagnostic accuracy of pre-treatment ADC (25, 26, 28, 30) for predicting the locoregional treatment response, and four investigating the diagnostic accuracy of change in ADC (9, 25, 33, 34).

### Characteristics of the Included Studies

The characteristics of the 12 included studies are listed in Table 1. The 12 original articles included ten prospective studies (9, 24, 25, 30, 33-38), one retrospective study (26), and one study with an unclear design (28). The target lesions of the studies were primary tumors (n = 3) (26, 30, 34), lymph nodes (n = 4) (24, 25, 28, 37), or both (n = 5) (9, 33, 35, 36, 38). Eleven studies investigated the value of pre-treatment ADC (9, 24-26, 28, 30, 34-38) for predicting locoregional treatment response, and ten studies investigated the value of change in ADC (9, 25, 28, 30, 33-38). All studies had a clear description of the reference standard for determining the treatment outcome, and detailed descriptions of the proportion of patients with locoregional failures and locoregional control. Among the total population of 418 patients, locoregional failure occurred in 136 patients (32.5%) and locoregional control was achieved in 282 patients (67.5%) (analysis per-patient).

All studies included pre-treatment MRI including DWI, and ten studies performed MRI at early intra-treatment or post-treatment periods, to evaluate the change in ADC value (9, 25, 28, 30, 33-38). The detailed technical characteristics of the MRI acquisitions are listed in Table 2. All of the DWI images were acquired in the axial plane using spin-echo echo-planar imaging sequences. The number of b-values used for the DWI ranged from one to ten, with majority of the studies using b-values between one and six (9, 24-26, 28, 30, 33-38). The regions of interest (ROIs) were outlined



**Fig. 1. Flow diagram of study selection process.** ADC = apparent diffusion coefficient

by experienced radiologists or oncologists, and were defined on either a single slice of the target lesion (24, 26, 30, 35-37), or on every section of all targeted lesions (9, 25, 28, 34, 38, 43).

### Quality Assessment

Overall, the quality of the studies was considered moderate, with 9 of the 12 studies satisfying at least 5 of the 7 QUADAS-2 domains (Fig. 2). Notable areas of quality concerns included no mention of blinding to the clinical outcomes of patients during ROI placement (24-26, 28, 34, 35, 37, 38). Regarding the patient selection domain, one study was considered to have a high risk of bias due to a non-consecutive case/control study design (26). In addition, one study was considered to have an unclear risk of bias as it did not explicitly mention whether patient enrollment was prospective or not (28). Only one study had a concern for applicability, which was because majority of the included patients were tested positive for human papillomavirus (HPV) (37). With regard to the reference standard and flow and timing domain, all studies were considered to have a low risk of bias.

### Pre-treatment ADC Value for Predicting Locoregional Treatment Response of HNSCC

Eleven studies investigated the value of pre-treatment ADC for predicting locoregional treatment response in patients with HNSCC (9, 24-26, 28, 30, 34-38). Of these 11 studies, 5 found that pre-treatment ADC values were significantly associated with locoregional treatment response (24-26, 28, 30); in all 5 of these studies, pre-treatment ADC values were significantly higher in patients with locoregional failure than in those with locoregional control. A cut-off ADC value ranging from 0.86 to 1.2 was mentioned in 4 studies (25, 26, 28, 30). In the other 6 studies that did not show a significant difference in ADC between the 2 groups, 2 studies showed lower values of pre-treatment ADC in locoregional control (9, 34), whereas in 3 studies, the pre-treatment ADC value was higher in the locoregional control (36-38). In 1 study, locoregional control showed higher ADC values than locoregional failure in primary tumors, but showed lower ADC values in lymph nodes (35). The diagnostic accuracy of pre-treatment ADC values for predicting locoregional failure was assessed in 4 studies (25, 26, 28, 30). Figure 3 is a forest plot of sensitivity and

**Table 1. Characteristics of Included Studies**

First Author (Publication Year) (Ref.)	Affiliated Institute	Study Period	No. of Patients	Mean Age, Year (Range)	Primary Tumor Location	Stage	Treatment	Outcome	Target Lesion	Timing of MRI	Follow-Up Period
Galbán (2009) (38)	University of Michigan Medical School, Ann Arbor, MI, USA	N/A	15	N/A	Oropharynx (12), nasopharynx (1), hypopharynx (1), unknown (1)	T1/2 (9), T3/4 (5), Tx (1), N0/1 (1), N2/3 (14)	CCRT	CR/PR	Primary tumor and lymph node	1 week before treatment, 3 weeks after initiation of treatment	6 months after initiation of treatment
Hatakenaka (2011) (30)	Kyushu University Hospital, Fukuoka, Japan	2006–2008	17	64 (37–85)	Oropharynx (7), hypopharynx (8), larynx (1), oral cavity (1)	T1/2 (7), T3/4 (10), N0/1 (5), N2/3 (12)	CCRT (13), RT (4)	Local control/failure	Primary tumor	8 days before treatment, 1 week after initiation of treatment	Local failure (4.6 months), local control (23.6 months)
		2006–2009	40	64 (37–85)	Oropharynx (15), hypopharynx (19), larynx (4), oral cavity (2)	T1/2 (21), T3/4 (19), N0/1 (14), N2/3 (26)	CCRT (35), RT (5)	Local control/failure	Primary tumor		Local failure (4.9 months), local control (16.4 months)
Kim (2009) (28)	University of Pennsylvania, Philadelphia, PA, USA	2005–2007	33	61 (N/A)	Oropharynx (21), larynx (7), unknown (5)	T0 (1), T1/2 (10), T3/4 (15), Tx (7), N0/1 (2), N2/3 (31)	CCRT (26), RT + immunotherapy (7)	CR/PR	Lymph node	Before treatment, 1 week after initiation of treatment, 2 weeks after completion of treatment	2 weeks after termination of treatment
King (2013) (34)	Hong Kong Cancer Institute and Prince of Wales Hospital, Shatin, Hong Kong SAR, China	2004–2008	37	57 (45–71)	Oral cavity or oropharynx (14), nasal cavity (2), hypopharynx or larynx (20), maxillary sinus (1)	T1/2 (9), T3/4 (28)	CCRT (33), RT (4)	Local control/failure	Primary tumor	Before treatment, 2 weeks after initiation of treatment, 6, 12, 18, 24 months after completion of treatment	Local failure (3.8 months), local control (43.9 months)
Lombardi (2017) (26)	Maggiore della Carita University Hospital, University of Eastern Piedmont, Corso Mazzini, Novara, Italy	2010–2014	47	59 (N/A)	Nasopharynx (23), oropharynx (19), hypopharynx (5)	T1/2 (14), T3/4 (33), N0/1 (21), N2/3 (26)	CCRT (39), neoadjuvant CTx + RT (8)	Local control/disease recurrence or persistence	Primary tumor	Before treatment	Disease recurrence or persistence (3–20 months), local control (10–36 months)
Marzi (2017) (25)	Regina Elena National Cancer Institute, Via Elio Chianesi, Rome, Italy	2010–2013	34	54.5 (28–79)	Oropharynx (14), nasopharynx (13), hypopharynx or larynx (6), unknown (1)	T0/1/2 (21), T3/4 (13), N1/2 (29), N3 (5)	CCRT	Regional control/failure	Lymph node	Before treatment, 16–17 days after initiation of treatment, immediately and 8 weeks after completion of treatment, per 6 months for 2 years, then annually	Regional failure (6.8 months), regional control (27.6 months)

**Table 1. Characteristics of Included Studies (continued)**

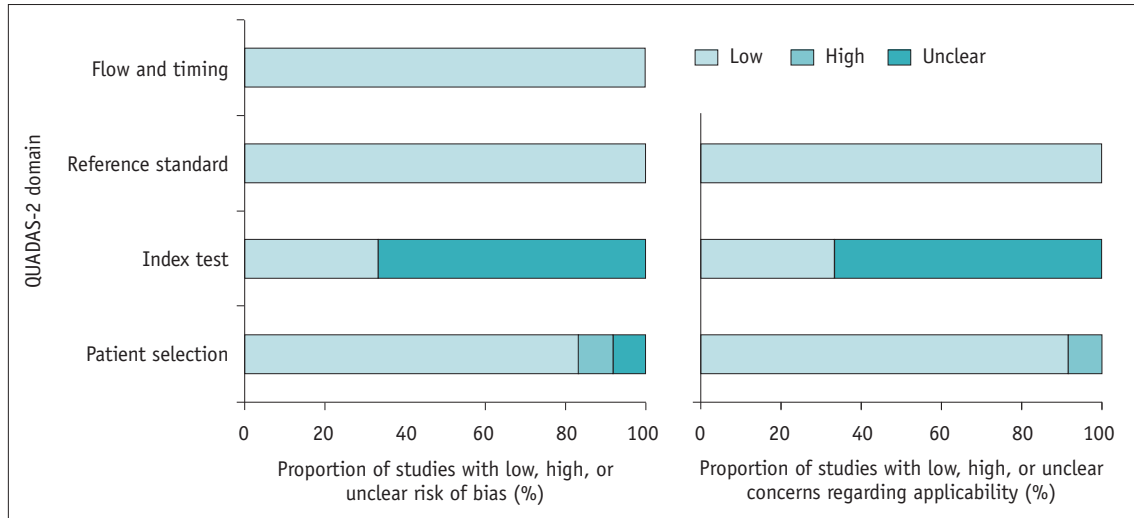
First Author (Publication Year) (Ref.)	Affiliated Institute	Study Period	No. of Patients	Mean Age, Year (Range)	Primary Tumor Location	Stage	Treatment	Outcome	Target Lesion	Timing of MRI	Follow-Up Period
Matoba (2014) (9)	Kanazawa Medical University, Ishikawa, Japan	2008–2012	35	66.5 (33–79)	Oropharynx (9), larynx (10), supraglottis (3), hypopharynx (9), oral cavity (4)	T1/2 (15), T3/4 (20), N0/1 (10), N2/3 (25)	CCRT	Locoregional control/failure	Primary tumor and lymph node	Before treatment, 3 weeks after initiation of treatment, then per 6 months	30.8 months
					Chang Gung Memorial Hospital, Chang Gung University, Kueishan, Taoyuan, Taiwan	2010–2012	69	50 (39–78)	Oropharynx (37), hypopharynx (32)	III (3), IVA (50), IVB (16)	CCRT
Paudyal (2017) (37)	Memorial Sloan Kettering Cancer Center, New York, NY, USA	2013–2015	34	N/A (32–82)	Oropharynx (32), unknown (2)	III (2), IVA (32)	CCRT (33), RT (1)	CR/non-CR	Lymph node	Before treatment, 1, 2, and 3 weeks after initiation of treatment	3–6 months after termination of treatment
Schouten (2014) (36)	VU University Medical Center, Amsterdam, Netherlands	N/A	8	60.9 (51–68)	Oropharynx (7), hypopharynx (1)	T2 (3), T3/4 (5), N1 (1), N2/3 (7)	CCRT	Regional control/failure	Primary tumor and lymph node	Before treatment, 14 days after initiation of treatment, per 3 months after completion of treatment	38 months
					University Hospitals Leuven, Herestraat, Leuven, Belgium	N/A	29	N/A	Oropharynx (15), hypopharynx (7), larynx (8)	T1/2 (7), T3/4 (23), N0/1 (11), N2/3 (18)	CCRT (26), RT (3)
Wong (2016) (35)	Royal Marsden NHS Foundation Trust, Sutton and London, UK	2013–2015	20	63 (47–69)	Oropharynx (18), hypopharynx/larynx (2)	T1/2 (11), T3/4 (9), N0/1 (2), N2/3 (18)	Induction CTx + CCRT	Responder/nonresponder	Primary tumor and lymph node	2 weeks after initiation of treatment	3 months after termination of treatment

CCRT = concurrent chemoradiation therapy, CR = complete response, CTx = chemotherapy, MRI = magnetic resonance imaging, N/A = not available, PR = partial response, RT = radiation therapy

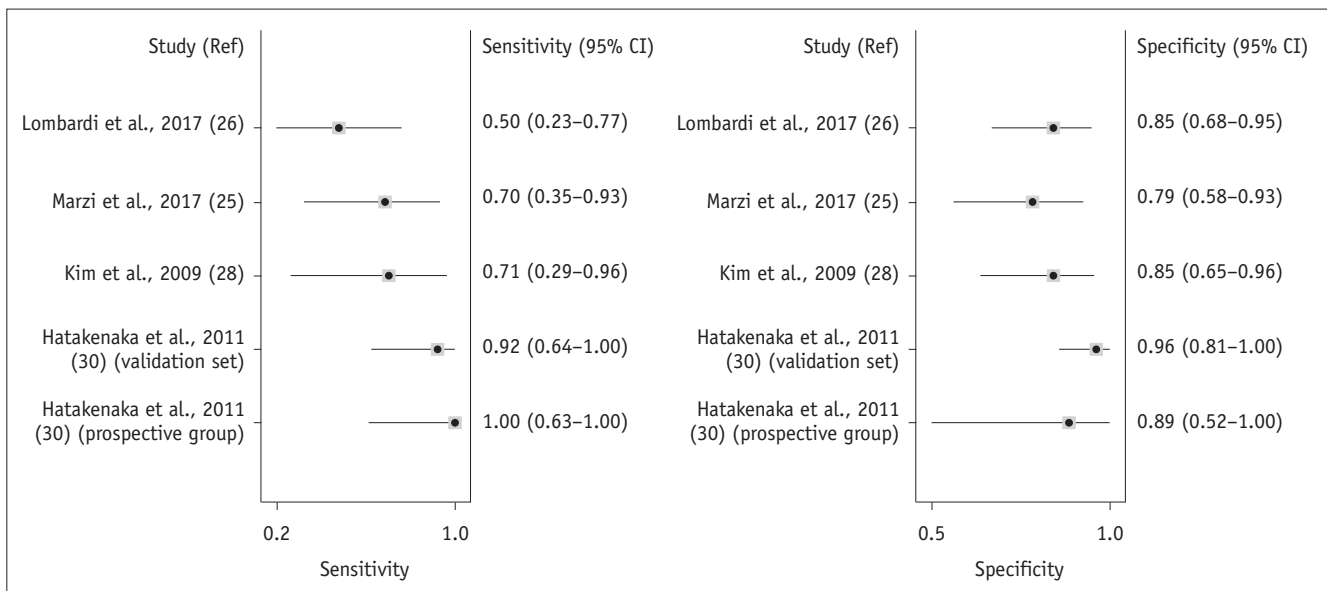
**Table 2. Technical Characteristics of Included Studies**

First Author (Year of Publication) (Ref.)	Vendor	Model	Field Strength (T)	DWI Sequence	Number of b-Values (Strength)	DWI Parameters	ROI Definition (Number Persons, Experience in Years)	ROI Extent	Blindness to Reference Standard
Galbán (2009) (38)	Philips	Achieva	3	SSEPI	2 (0, 800)	TR/TE = 5000/77-100, NEX: 2, FOV: 240 x 192 mm, slice thickness: 6 mm, time: 5 min, matrix: 120 x 97	Radiologist or oncologist (2, N/A)	Volume	N/A
Hatakenaka (2011) (30)	Philips	Intera Achieva	1.5	SSEPI	7 (0, 100, 200, 300, 500, 750, 1000)	TR/TE = 3000/73, NEX: 2, bandwidth: 1645.9, time: 4 min 6 sec, matrix: 256 x 112	Radiologists (2, > 15 yr)	Single section	Yes
Kim (2009) (28)	Siemens	Sonata, Trio	1.5 or 3	SSEPI	3 (0, 500, 1000)	TR/TE = 4000/89, signal average: 4	Radiologist (1, N/A)	Volume	N/A
King (2013) (34)	Philips	Intera NT	1.5	SSEPI	6 (0, 100, 200, 300, 400, 500)	TR/TE = 2000/75, slice thickness: 4 mm, gap: 0, FOV: 230 mm, acquisition matrix: 112 x 112, reconstruction matrix: 256 x 256, signal average: 4	Radiologist (1, > 15 yr)	Volume	N/A
Lombardi (2017) (26)	Philips	Achieva	1.5	EPI	3 (0, 500, 1000)	N/A	Radiologist (1, 5 yr)	Single section	N/A
Marzi (2017) (25)	GE Healthcare	Optima	1.5	SSEPI	9 (0, 25, 50, 75, 100, 150, 300, 500, 800)	TR/TE = 4500/77, slice thickness: 4 mm, gap: 5 mm, bandwidth: 1953, FOV: 260-280 mm, acquisition matrix: 128 x 128, time: 6 min 13 sec	Radiologists (2, 15, and 6 yr)	Volume	N/A
Matoba (2014) (9)	Siemens	Avanto	1.5	SSEPI	3 (0, 90, 800)	TR/TE = 4000/68, TI: 180, matrix: 512 x 256, FOV: 25, section thickness: 6 mm, gap: 3 mm	Radiologists (2, 15, and 20 yr)	Volume	Yes
Ng (2014) (24)	Siemens	Magnetom Trio with TIM	3	SSEPI	2 (0, 800)	TR/TE = 8200/84, time: 2 min 28 sec, slice thickness: 5 mm	Radiologist (1, > 20 yr)	Single section	N/A
Paudyal (2017) (37)	Philips	Ingenia	3	SSEPI	10 (0, 20, 50, 80, 200, 300, 500, 800, 1500, 2000)	TR/TE = 4000/minimum, NA: 2, matrix: 128 x 128, FOV: 20-24, slices: 8-10, slice thickness: 5 mm, time: 5 min	Radiation oncologist (1, > 5 yr) and radiologist (1, > 10 yr)	Single section	N/A
Schouten (2014) (36)	Siemens	Sonata	1.5	EPI, HASTE	3 (0, 500, 1000)	TR/TE = 5000/105, in-plane pixel size: 2 x 2 mm	Radiologist (1, 29 yr)	Single section	Yes
Vandecaveye (2012) (33)	Siemens	SONATA Vision	1.5	SSEPI	6 (0, 50, 100, 500, 750, 1000)	TR/TE = 7100/84, matrix: 104 x 128, 44 slices, slice thickness: 4 mm, gap: 0.4 mm, FOV: 20 x 25	Radiologist (1, 6 yr)	Volume	Yes
Wong (2016) (35)	Siemens	MAGNETOM Aera	1.5	SSEPI	3 (50, 400, 800)	TR/TE = 13400/61, matrix: 96, FOV: 199 x 199, bandwidth: 1000	Radiation oncologist (1, N/A) and radiologist (1, N/A)	Single section	N/A

DWI = diffusion-weighted imaging, EPI = echo-planar imaging, FOV = field of view, HASTE = Half fourier Single-shot Turbo spin-Echo, NA = number of averages, NEX = number of excitations, ROI = region of interest, SSEPI = single-shot spin-echo EPI, T = tesla, TE = echo time, TI = inversion time, TR = repetition time



**Fig. 2. QUADAS-2 criteria for included studies.** QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies-2



**Fig. 3. Forest plots of sensitivity and specificity of pre-treatment ADC for prediction of locoregional recurrence.** Horizontal lines indicate 95% CIs of individual studies. CI = confidence interval, Ref = reference

specificity for the 4 included studies. The coupled forest plots of the sensitivity and specificity for the pre-treatment ADC did not reveal any apparent threshold effect and the Spearman correlation coefficient between sensitivity and false-positive rate was -0.519 (95% confidence interval [CI], -0.961–0.670). Meta-analytic pooling of the sensitivity and specificity values was not performed due to the apparent heterogeneity in these values that were unexplainable with threshold effect, and infeasibility of robust analysis of the causes of heterogeneity. The total population comprised of 171 patients, with 52 patients (30.4%) having locoregional failure. The sensitivities and specificities of the 4 individual

studies ranged from 50% to 100% and from 79% to 96%, respectively (Table 3).

### Change in ADC Value for Predicting Locoregional Failure of HNSCC

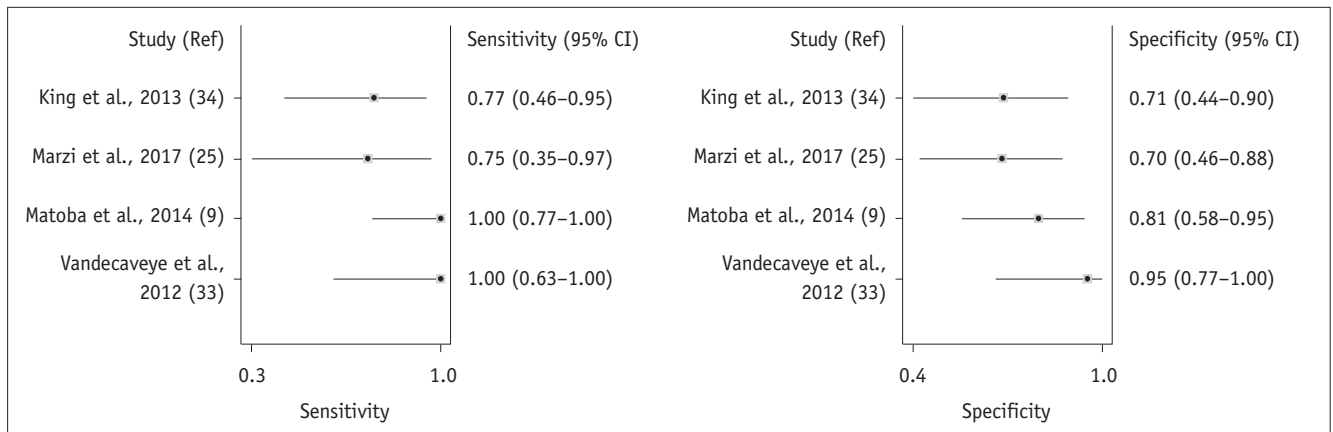
Ten studies investigated the value of change in ADC for predicting locoregional treatment response in HNSCC (9, 25, 28, 30, 33–38). In all 10 studies, the change in ADC was larger in the patients with locoregional control than in those with locoregional failure, and 5 studies showed a statistically significant difference (9, 28, 30, 33, 34). The cut-off value for change in ADC was mentioned in 4



**Table 3. Summary of Diagnostic Accuracy of Pre-Treatment ADC Value in Predicting Locoregional Failure in HNSCC**

Study	Total	TP	FP	FN	TN	Sensitivity	Specificity
Hatakenaka et al., 2011 (30) (prospective group)	17	8	1	0	8	1.00	0.89
Hatakenaka et al., 2011 (30) (validation set)	40	12	1	1	26	0.92	0.96
Kim et al., 2009 (28)	33	5	4	2	22	0.71	0.85
Marzi et al., 2017 (25)	34	7	5	3	19	0.70	0.79
Lombardi et al., 2017 (26)	47	7	5	7	28	0.50	0.85

ADC = apparent diffusion coefficient, FN = false negative, FP = false positive, HNSCC = head and neck squamous cell carcinoma, TN = true negative, TP = true positive



**Fig. 4. Forest plots of sensitivity and specificity of change in ADC for prediction of locoregional recurrence.** Horizontal lines indicate 95% CIs of individual studies.

**Table 4. Summary of Diagnostic Accuracy of Change in ADC Value in Predicting Locoregional Failure in HNSCC**

Study	Total	TP	FP	FN	TN	Sensitivity	Specificity
Vandecaveye et al., 2012 (33)	30	8	1	0	21	1.00	0.95
Matoba et al., 2014 (9)	35	14	4	0	17	1.00	0.81
Marzi et al., 2017 (25)	28	6	6	2	14	0.75	0.70
King et al., 2013 (34)	30	10	5	3	12	0.77	0.71

studies, and ranged from 15.5% to 25% (9, 25, 33, 34). The time over which the change in ADC was measured ranged from one to three weeks from the start of CCRT, except for one study where the ADC was measured three weeks after completion of CCRT (33). The diagnostic accuracy of the change in ADC for predicting locoregional failure was assessed using 4 studies (9, 25, 33, 34). The coupled forest plots of sensitivity and specificity for the change in ADC did not reveal any apparent threshold effect and the Spearman correlation coefficient between sensitivity and false-positive rate was -0.829 (95% CI, -0.996-0.650). (Fig. 4). Meta-analytic pooling of the sensitivity and specificity values was not performed for the same reasons as those mentioned above. The total population comprised of 135 patients, with locoregional failure in 43 (31.9%). The sensitivities and specificities of the 4 individual studies ranged from 75% to 100% and from 69% to 95%, respectively (Table 4).

## DISCUSSION

In the current systematic review, we demonstrated that high pre-treatment ADC and a low rise in ADC during the early intra-treatment or post-treatment periods of CCRT were indicators of locoregional failure in patients with HNSCC. Considering the consistency in the results of change in ADC obtained, we propose that it could be a promising approach to predict treatment response after CCRT.

In clinical practice, an accurate prediction of disease progression after treatment could be extremely useful for selecting the appropriate adjuvant treatment and improving the patient's prognosis (9). Cases of HNSCCs with high stromal content, low cellularity, and micronecrosis are associated with resistance to treatment and poor outcome (44). These tumor characteristics decrease diffusion of water molecules (45-47), and therefore it is

hypothesized that high ADC is a predictor of poor outcome. However, the results from using pre-treatment ADC for the prediction of locoregional failure are inconsistent. The treatment response may be attributed to differences in tumor aggressiveness, HPV status, treatment protocol, or the intensity of treatment, and hence, the use of only a single ADC measurement at pre-treatment appears to be inadequate for the prediction of treatment response (9, 35).

As response-adapted therapy becomes more widespread in cancer management, there will be greater interest in performing intra-treatment scanning (44). Increase in ADC during treatment has been correlated with the histological presence of necrosis, apoptosis, and inflammation (33, 48), and is thought to be a useful predictor of treatment response. All of the 10 studies that investigated the role of change in ADC at early intra-treatment or post-treatment periods found consistent results (9, 25, 28, 30, 33-38). A lower rise in the mean ADC was found at one to three weeks after the start of treatment in patients with locoregional failure, compared to that in patients with locoregional control. This approach may be more appropriate because the change in ADC is more objective and reproducible across centers than absolute ADC values (i.e., pre-treatment ADC) (44). In many malignant tumors, it is well known that successful treatment is correlated with an increase in ADC values (49-53). Additionally, the ability of DWI to predict treatment outcome at one to three weeks after the start of treatment seems to be in agreement with the expected optimal timing of adjuvant neck dissection after CCRT or radiotherapy (54-56).

Heterogeneity was not quantified since it is an expected flaw in systematic reviews of diagnostic test accuracy. Instead, the possible sources for heterogeneity were explored. First, among the 12 studies, 3 acquired data from the primary tumors (26, 30, 34), 4 from lymph nodes (24, 25, 28, 37), and 5 from both sites (9, 33, 35, 36, 38). The study by Wong et al. (35) found that mean pre-treatment ADC values were higher in locoregional control than in locoregional failure in primary tumors, but found opposite results in lymph nodes. It may be related to the fact that ADC values acquired from the primary sites may be more influenced by physiologic motion and susceptibility artifacts than those acquired from cervical lymph nodes (9). Second, the included studies used different numbers and distributions of b-values, with majority of the studies using one to six b-values (9, 24, 26, 28, 30, 33-36, 38), although 2 studies used nine or ten b-values (25, 37).

Recent studies show that mean ADCs obtained from high b-value ranges of 300–1000 s/mm<sup>2</sup> are more appropriate for predicting treatment response than mean ADCs obtained from low b-value ranges of 0–300 s/mm<sup>2</sup> (27, 30, 44, 57). Finally, the HNSCC showed heterogeneous histopathology with areas of micronecrosis, even though it was not readily distinguishable on imaging. Therefore, the use of the mean ADC of the whole tumor is considered more accurate than the measurement from a single section ROI (9).

The prediction of tumor response with ADC offers several advantages over the use of other imaging modalities like <sup>18</sup>F-FDG PET/CT, contrast-enhanced MRI, magnetic resonance spectroscopy, and dynamic contrast-enhanced MRI. These include: absence of the need for injection of an isotope or contrast agent, short acquisition time, and simple estimation. Despite these advantages of ADC, the clinical use of ADC for the prediction of tumor response in HNSCC presents challenges due to susceptibility and motion artifacts. Furthermore, there is no clear threshold for the differentiation between locoregional failure and locoregional control. Finally, different MRI systems and different b-values have been used in previous studies. This means that the use of ADC cannot be extrapolated across hospital sites. Thus, further clinical studies to standardize and validate ADC measurements are necessary.

This study was limited by the relatively few included studies and its potential heterogeneity. This precluded our ability to perform meta-analysis, analyze subgroups, and identify potentially important covariates. When sufficient papers have been published in the future, a meta-analysis considering the factors that may cause heterogeneity may be performed.

In conclusion, high pre-treatment ADC and a low rise in ADC during the early intra-treatment or post-treatment periods of CCRT could be indicators of locoregional failure in patients with HNSCC. Considering the consistency of the results obtained with change in ADC, we propose that it could be used to identify patients who require more aggressive investigations to identify any residual cancer. However, as the studies are few, heterogeneous, and at high risk for bias, the sensitivity and specificity of these parameters for predicting treatment response are yet to be determined. Continued research on standardization and validation of ADC measurement, and determination of the optimal threshold for percentage change, are required for clinical use.

### Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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