

Meta-analysis of diffusion-weighted imaging for predicting locoregional failure of chemoradiotherapy in patients with head and neck squamous cell carcinoma

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Received July 21, 2017; Accepted October 24, 2017

DOI: 10.3892/mco.2017.1504

Abstract. The purpose of this study was to evaluate the accuracy of diffusion-weighted imaging (DWI) for predicting locoregional failure of chemoradiotherapy in patients with head and neck squamous cell carcinoma (HNSCC). A comprehensive search was conducted through the EMBASE, PubMed and Cochrane Library databases for relevant publications. Stata software was used to calculate the pooled sensitivity, specificity, likelihood ratios and diagnostic odds ratios, and to construct a summary receiver operating characteristics (sROC) curve for DWI. A total of 9 studies comprising 421 patients were included. The pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio and diagnostic odds ratio were 0.82 [95% confidence interval (CI): 0.72-0.88], 0.70 (95% CI: 0.62-0.77), 2.7 (95% CI: 2.1-3.6), 0.26 (95% CI: 0.17-0.41), and 10.48 (95% CI: 5.35-20.53), respectively. The area under the sROC curve was 0.84 (95% CI: 0.81-0.87). Therefore, DWI appears to be a promising imaging modality for predicting local failure of chemoradiotherapy in patients with HNSCC.

Introduction

Head and neck squamous cell carcinoma (HNSCC) accounts for ~3% of all malignancies (1). Currently, chemoradiotherapy (CRT) is considered as a good approach to the treatment of

locally advanced HNSCC. However, ~25-30% of patients have local residual disease or develop relapse at the primary or lymph node sites after treatment (2), which represents a challenge in the management of HNSCC. Therefore, there is a need for biomarkers that can provide accurate and timely prediction of therapeutic outcome prior to treatment or in the early stages of treatment, with discontinuation of ineffective approaches and timely application of alternative therapeutic strategies.

Recently, diffusion-weighted imaging (DWI) was proposed as an imaging biomarker for predicting treatment outcome in multiple malignancies, including rectal cancer (3), breast cancer (4) and glioblastoma (5). DWI quickly measures the Brownian motion of extracellular water molecules in biological tissues, which may be quantified with the apparent diffusion coefficient (ADC) (6). Previous studies demonstrated that higher pretreatment ADCs were correlated with poor response to treatment (7,8). In addition, due to its ability to depict the range of ADCs, ADC histograms may be used to evaluate the heterogeneity of the whole tumor. This feature enables evaluation of the degree of necrosis and viability, which may be crucial when planning a radiation dose boost (9).

Over the past few years, a number of studies have investigated the role of DWI in predicting response to CRT in patients with HNSCC. Given the varied characteristics of the patients and studies, individual studies are unable to provide a reliable estimate of DWI performance for the prediction of treatment response. Hence, the present meta-analysis was performed to determine the diagnostic performance of DWI for the prediction of locoregional failure of CRT in patients with HNSCC, which may be helpful in optimizing the management of this disease.

Data collection methods

Search strategy. A comprehensive search was conducted through the EMBASE, PubMed and Cochrane Library databases to identify relevant publications on the accuracy of DWI in the prediction of response to CRT in patients

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Key words: head and neck squamous cell carcinoma, chemoradiotherapy, diffusion-weighted imaging, locoregional failure

with HNSCC. The Emtree terms (for EMBASE), medical subject heading terms (for Medline), and text words (for other databases) included ('head and neck cancer' OR 'head and neck neoplasms' OR 'lip cancer' OR 'lip neoplasms' OR 'oropharynx cancer' OR 'oropharyngeal neoplasms' OR 'hypopharyngeal cancer' OR 'hypopharyngeal neoplasms' OR 'nasopharynx cancer' OR 'nasopharyngeal neoplasms' OR 'laryngeal cancer' OR 'laryngeal neoplasms' OR 'salivary gland cancer' OR 'salivary gland neoplasms') AND ('diffusion weighted magnetic resonance imaging' OR 'diffusion weighted MRI' OR 'diffusion MRI' OR 'DWI') AND ('concurrent chemoradiotherapy' OR 'synchronous chemoradiotherapy' OR 'concomitant chemoradiotherapy' OR 'chemoradiotherapy' OR 'radiotherapy'). The search was updated on March 21, 2017. To extend the search, the reference lists of the articles that were identified after the selection process were screened for additional suitable articles.

Study selection. Studies were considered eligible for inclusion if the accuracy of DWI in the prediction of response to CRT was investigated in patients with HNSCC. The eligible studies were also required to have a defined reference standard for local failure, which included residual disease and local recurrence. Accordingly, local failure was required to be histopathologically confirmed, or at least clinically suspected, in terms of the presence of any mass or a persisting and/or increasing existing residual mass on serial imaging during follow-up. In addition, the studies had to include at least 25 patients and yield sufficient information, including true and false positive and negative values, in order to construct a 2x2 contingency table to calculate sensitivity and specificity in the prediction of local failure. Moreover, only articles published in English were included. Review articles, comments, letters, case reports and animal experiments were excluded. When overlapping data from the same authors were presented among different articles, the article with the most recent details or the largest number of patients was selected.

Data extraction and quality assessment. Two reviewers (Q.M.Z. and Y.D.) independently extracted the relevant data and assessed the quality of the retrieved studies. To resolve discrepancies between the two reviewers, a consensus meeting was held; if agreement could not be reached, a third reviewer (F.F.Z.) was consulted. The extracted data were as follows: Patient characteristics (sample size, mean or median age and range), study characteristics [first author, publication year, country of origin, study design (prospective, retrospective or unknown), patient enrollment (consecutive or not), whether blinding was used in the study, number of patients, tumor location, TNM stage, number of reviewers, radiotherapy regimen and chemotherapy regimen], and technical details of magnetic resonance imaging (MRI) protocols [magnetic field strength, repetition time/echo time (TR/TE), MRI vendor, slice thickness, field of view (FOV), matrix and b value]. The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) was used to assess the methodological quality of the included studies. QUADAS-2 has four key domains: Patient selection, index test, reference standard, and flow and timing.

Statistical analysis. A meta-analysis was performed using Stata software, version 13.0 (Stata Corp., College Station,

TX, USA). Data were combined to obtain pooled sensitivity, specificity, diagnostic odds ratios (DORs) and likelihood ratios (LRs). A summary receiver operating characteristics (sROC) curve was constructed and the area under the curve (AUC) obtained. An inconsistency index (I^2) test was performed to assess the heterogeneity between studies. An I^2 value $>50\%$ indicated heterogeneity, in which case a random-effects model was used; otherwise, a fixed-effects model was applied. As an important source of heterogeneity, the threshold effect was assessed by calculating the Spearman's correlation coefficient. If there was no threshold effect, a meta-regression analysis was then performed to investigate other potential sources of heterogeneity. Publication bias was investigated by constructing a Deeks' funnel plot. P-values of <0.05 were considered to indicate statistically significant differences.

Results

Literature search and study selection. Our database search and extensive reference list cross-check yielded 365 studies. After excluding duplicates and reviewing the titles and abstracts, 65 studies remained, and their full texts were retrieved. After the full texts were reviewed, 56 studies were excluded for the following reasons: Patient number <25 ($n=19$); the same data were presented in another article by the same group ($n=5$); the studies were reviews, letters, or proceedings of a symposium ($n=19$); the articles were not written in English ($n=9$); and sufficient data were not extractable to construct a 2x2 contingency table to calculate sensitivity and specificity in the prediction of local failure ($n=4$). Ultimately, a total of 9 eligible studies involving 421 patients were included in the meta-analysis (7,8,10-16). A search of the reference lists of these eligible articles did not yield other potentially relevant articles.

Study description. The detailed characteristics of the 9 included studies are summarized in Tables I and II. The median number of patients per study was 37 (range, 26-134). Of the 9 studies, 6 enrolled patients prospectively and 3 retrospectively. A total of 4 studies enrolled patients consecutively, whereas the remaining 5 studies enrolled patients in an unknown manner. In 4 studies, treatment response was assessed by reviewers who had been blinded to the results of the DWI analysis; in the other 5 studies, this detail was not provided. In 8 studies, DWI examinations were conducted with 1.5 T devices, whereas in 1 study, both 3.0 T and 1.5 T devices were used.

Assessment of study quality. The QUADAS-2 scores of each study are listed in Table III. The quality of the 9 studies varied. A total of 4 studies had a low risk of bias regarding patient selection, whereas 5 studies had an unclear risk of bias due to insufficient information. All 9 studies reported a low risk of bias regarding the index test. The risk of bias regarding the reference standard was low in 4 studies and unclear in 5 studies, as the latter studies provided insufficient information on blinding. The risk of bias regarding flow and timing was low in 4 studies and high in 5 studies, as different reference standards were applied during follow-up in the latter studies. As regards risk in applicability, all 9 studies had a low risk of bias.

Table I. Patient and study characteristics.

Authors	Year	Country	Study design	Patient enrollment	Blinding status	No. of patients	Mean/median age, years (range)	Tumor location	TNM stage(s)	Reviewers (experience)	Radiotherapy regimen	Chemotherapy regimen	(Refs.)
Xiao-ping <i>et al</i>	2016	China	Prospective	Consecutive	Blind	50	48.9±11.1	Nasopharynx	T2-4N0-3M0-1	Two radiologists (5 and 20 years)	7,000-7,600 cGy/30-33 f	TN, TNF, NF	(10)
Scalco <i>et al</i>	2016	Italy	Retrospective	NA	NA	30	NA	HNSCC ^a	T1-4N1-3	One radiologist (15 years)	7,000 cGy /33 f	Cisplatin	(11)
Hou <i>et al</i>	2016	China	Prospective	Consecutive	Blind	43	49.0 (26-68)	Nasopharynx	T2-4N0-3M0	Two radiologists (>10 years)	7,000-7,600 cGy/30-33 f	TN	(12)
Hong <i>et al</i>	2013	China	Prospective	NA	NA	134	47.0 (18-79)	Nasopharynx	T1-4	NA	6,600-7,875f cGy/30-33	TP, cisplatin	(14)
King <i>et al</i>	2013	China	Prospective	Consecutive	NA	37	57.0 (45-71)	HNSCC ^b	III-IV	One radiologist (>15 years)	NA	NA	(13)
Nakajo <i>et al</i>	2012	Japan	Retrospective	NA	NA	26	65.0 (45-89)	HNSCC ^c	T1-4N0-3	NA	6,000 cGy/30 f	NA	(15)
Hatakenaka <i>et al</i>	2011	Japan	Retrospective	NA	Blind	38	64.0 (37-85)	HNSCC ^d	T1-4N0-3	Two radiologists (unknown)	6,000 cGy	S-1, cisplatin	(8)
Vandecaveye <i>et al</i>	2010	Belgium	Prospective	Consecutive	Blind	30	53.0 (38-66)	HNSCC ^e	T1-4N1-3	One radiologist (6 years)	7,200 cGy	NA	(16)
Kim <i>et al</i>	2009	USA	Prospective	NA	NA	33	61.0±10.8	HNSCC ^f	T0-4N1-2bM0	NA	7,040 cGy/32 f	Cisplatin	(7)

^aOropharynx, nasopharynx, hypopharynx, larynx, and unknown primary. ^bOropharynx, hypopharynx, larynx, nasal cavity, oral cavity, and maxillary sinus. ^cOropharynx, nasopharynx, hypopharynx, larynx, oral cavity and maxillary sinus. ^dOropharynx, hypopharynx, larynx and oral cavity. ^eOropharynx, tonsil, base of tongue, supraglottic, glottic and piriform sinus. ^fLarynx, vallecula, tonsil, base of tongue and unknown primary. NA, not available; HNSCC, head and neck squamous cell carcinoma; TN, Taxol + nedaplatin; TNF, nedaplatin + 5-fluorouracil; NF, nedaplatin + 5-fluorouracil; TP, Taxol + cisplatin.

Table II. Technical details of MRI protocols.

Authors	Magnet strength (T)	TR/TE (msec)	MRI vendor	Slice thickness (mm)	FOV (mm)	Matrix	b value (sec/mm ²)	(Refs.)
Xiao-ping <i>et al</i>	1.5	4,225/106	GE	5	Unknown	128x130	0, 200, 400, 600, 800, 1,000	(10)
Scalco <i>et al</i>	1.5	4,500/77	GE	4	260-280	128x128	0, 500, 800	(11)
Hou <i>et al</i>	1.5	4,225/106	GE	5	220	128x130	0, 50, 80, 100, 150, 200, 400, 600, 800, 1,000	(12)
Hong <i>et al</i>	1.5	Unknown	GE	Unknown	240x240	128x128	0, 800	(14)
King <i>et al</i>	1.5	2,000/75	Philips	4	230	112x112	0, 100, 200, 300, 400, 500	(13)
Nakajo <i>et al</i>	1.5	6,000/68	Siemens	6	370	112x168	0, 800	(15)
Hatakenaka <i>et al</i>	1.5	3,000/73	Philips	3-5	200-230	112x79	0, 300, 1,000	(8)
Vandecaveye <i>et al</i>	1.5	7,100/84	Siemens	4	200x250	104x128	0, 50, 100, 500, 750, 1,000	(16)
Kim <i>et al</i>	1.5 or 3.0 ^a	4,000/89	Siemens	5	260	NA	0, 500, 1,000	(7)

^a1.5 T (n= 24), 3.0 T (n=9); NA, not available; MRI, magnetic resonance imaging; TE, echo time; TR, repetition time.

Table III. Quality assessment of included studies: Summarized risk of bias and applicability concerns.

Authors	Risk of bias				Applicability			(Refs.)
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard	
Xiao-ping <i>et al</i>	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	(10)
Scalco <i>et al</i>	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	(11)
Hou <i>et al</i>	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	(12)
Hong <i>et al</i>	Unclear risk	Low risk	Unclear risk	High risk	Low risk	Low risk	Low risk	(14)
King <i>et al</i>	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	(13)
Nakajo <i>et al</i>	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	(15)
Hatakenaka <i>et al</i>	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	(8)
Vandecaveye <i>et al</i>	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	(16)
Kim <i>et al</i>	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	(7)

Meta-analysis. The sensitivity and specificity of DWI in the prediction of locoregional failure of CRT in HNSCC patients ranged from 0.69 to 0.95 and from 0.55 to 0.89, respectively, with pooled estimates of 0.82 [95% confidence interval (CI): 0.72-0.88] and 0.70 (95% CI: 0.62-0.77), respectively. The forest plots of sensitivities and specificities are shown in Fig. 1. Using the sROC curve, the AUC was 0.84 (95% CI: 0.81-0.87; Fig. 2). The positive LR, negative LR and the DOR of DWI were 2.7 (95% CI: 2.1-3.6), 0.26 (95% CI: 0.17-0.41) and 10.48 (95% CI: 5.35-20.53), respectively. Among all 9 studies, no significant heterogeneity was found in terms of pooled sensitivity ($P=0.42$, $I^2=1.4\%$), specificity ($P=0.05$, $I^2=48.06\%$), or DOR ($P=0.26$, $I^2=20.6\%$). The Deeks' funnel plot asymmetry test revealed no strong evidence for publication bias ($P=0.10$; Fig. 3).

Discussion

The present meta-analysis investigated the feasibility of ADC as an imaging biomarker for the assessment of locoregional failure of CRT in HNSCC patients. Accurate prediction or monitoring of therapeutic efficacy before or during the early stages of treatment is crucial for individual patients to modify the ongoing treatment regimen in a timely manner. In addition, patients with radioresistant tumors may be offered an escalated radiation dose or alternative treatment options, such as early surgical intervention.

To the best of our knowledge, this is the first meta-analysis to determine the ability of DWI to predict local failure of CRT in HNSCC patients. A pooled sensitivity of 0.82 (95% CI: 0.72-0.88) and a specificity of 0.70 (95% CI: 0.62-0.77)

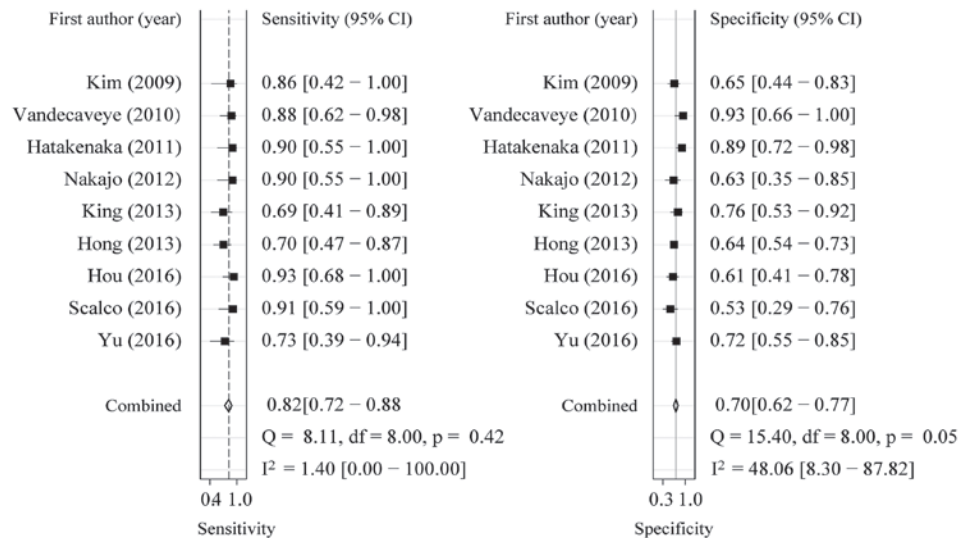


Figure 1. Forest plots of sensitivity and specificity with corresponding 95% confidence intervals for diffusion-weighted imaging to predict locoregional failure of chemoradiotherapy in patients with head and neck squamous cell carcinoma. CI, confidence interval; df, degree of freedom.

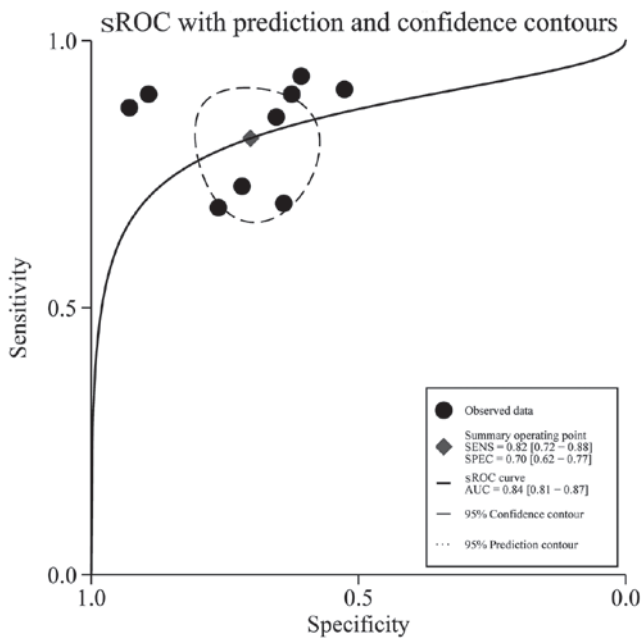


Figure 2. Summary receiver operating characteristic (sROC) curve for all 9 studies. The area under the ROC curve (AUC) of the apparent diffusion coefficient (ADC) was 0.84 (95% confidence interval: 0.81-0.87), indicating good accuracy in predicting locoregional failure of chemoradiotherapy in patients with head and neck squamous cell carcinoma. SENS, sensitivity; SPEC, specificity.

were calculated from a total of 421 patients in 9 studies who fulfilled all the inclusion and exclusion criteria. Furthermore, according to a widely accepted interpretation (17), a good predictive accuracy (AUC=0.84) was observed between local failure and locally controlled lesions.

A number of studies have investigated the role of DWI in the prediction of response to therapeutic interventions. A preclinical study by Hamstra *et al* (18) reported that a significant increase in ADC was noted in an animal model of HNSCC 5 days after initiation of CRT, which may be used as a marker to predict treatment response. Kim *et al* (7) also reported that

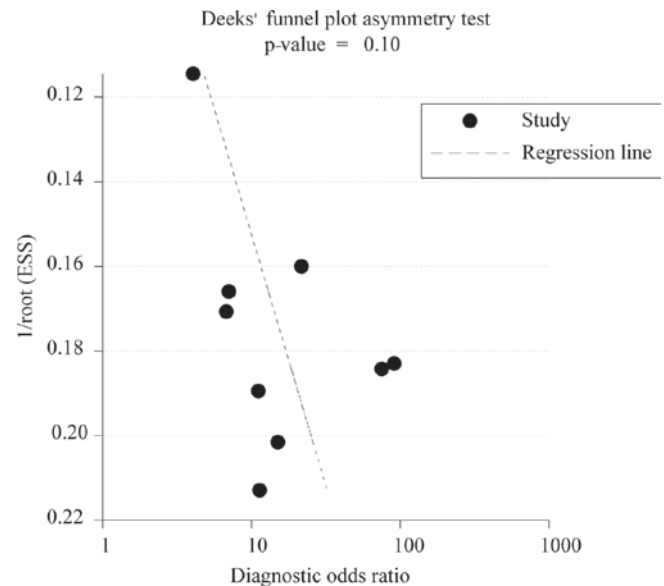


Figure 3. Results of Deeks' funnel plot from the asymmetry test for publication bias. The non-significant slope indicates that no significant bias was observed. ESS, effective sample size.

patients with complete response to CRT had significantly lower pretreatment ADC values than did patients with partial response. In addition, the changes in ADC between baseline and early intratreatment measurement may also demonstrate higher test accuracy in separating favorable from unfavorable responders. Contrary to Kim *et al*, King *et al* (19) reported that ADC values were more effective after treatment, compared with before or during treatment, in predicting response to CRT in HNSCC patients. All these studies indicated that ADC may be used as an important imaging biomarker for personalized treatment in HNSCC.

From a clinical perspective, optimized clinical benefit may be achieved by adopting the most appropriate treatment strategies or timely modification of a treatment plan on the basis of an individual patient's response assessment.

Therefore, ADC values have been proposed to be of higher value as biomarkers before treatment or in early intra-treatment than they are in a post-treatment setting. In our meta-analysis, only studies using either pretreatment ADC ($n=6$) (7,8,10-12,15) or percentage change in ADC values between baseline and early intratreatment measurement ($n=3$) (13,14,16) were included to predict locoregional failure of CRT in HNSCC patients, with the optimum cutoff (threshold) values for ADC ranging from 0.86 to 1.11 for pretreatment and from 14 to 52.7% for percentage change in ADC. According to the histopathological analysis (20), high numbers of tumor-stromal cells, which contribute to reducing the restriction of water molecule motion in tumors, are significantly associated with high pretreatment ADC values. Stromal cells play a crucial role in supporting the growth of tumors by promoting tumor cell invasion, protecting apoptosis, and then creating a barrier to systemic therapy. This may partly explain the biological mechanisms underlying the association between high pretreatment ADC values and poor treatment response to CRT in HNSCC patients.

Currently, in addition to DWI, multiple imaging modalities, including dynamic contrast-enhanced MRI (21), phosphorous MR spectroscopy (22), and fluorine-18-fluorodeoxyglucose positron emission tomography with computed tomography (23) have been used to predict and monitor treatment efficacy in HNSCC patients. The notable advantages of DWI over these other imaging modalities are its simplicity and the fact that the use of contrast agents is not required. Injection of contrast agents may increase the cost and their use may not be indicated in patients who have severe renal function impairment. Therefore, it is more advantageous to use DWI to predict and monitor the treatment response.

Several limitations should be acknowledged in this meta-analysis. First, the number of included studies and samples was moderate. This limitation may lead to an over-estimation of predictive accuracy (24). Second, the reference standards regarding locoregional failure of CRT included histopathological findings or clinical and imaging results during the follow-up period, which may affect the predictive value of DWI. Third, although the heterogeneity among the included studies was not significant, it was present. Human papillomavirus (HPV) status was not detailed in all the included studies. HPV status is the primary etiological determinant of chemoradiotherapy response, demonstrating a 25% improvement in 3-year overall survival in large-scale cooperative group datasets (25). While not exclusively HPV-associated, domestically, the vast majority of oropharyngeal cancers are HPV-related (26). However, at present, HPV status does not define a differential in terms of standard of care treatment, which remains CRT for the majority of head and neck cancers. Consequently, pooled analysis is appropriate until results from cooperative group studies (such as NRG HN002) (27) are mature enough to define whether HPV status-based de-intensification is efficacious. Finally, factors associated with the scanning protocol and analysis method differed among the studies. To further establish DWI as a routine clinical assessment tool, DWI scanning methods and analysis protocols should be validated or standardized. Recently, the Radiological Society of North America Quantitative Imaging Biomarker Alliance have

developed a standardized ADC measurement phantom (28). The use of this device to standardize ADC measurements across facilities/devices/sequences is imperative for future DWI implementation.

In conclusion, our meta-analysis suggests that DWI is a promising imaging modality for predicting local failure of CRT in HNSCC patients. However, considering the limitations of the present study, the results must be interpreted with caution. Larger-scale, prospective, randomized-controlled studies are required to confirm the clinical value of DWI in predicting treatment outcome in HNSCC.

Acknowledgements

The authors would like to thank Mrs. Tamara K. Locke at the Department of Scientific Publications of MD Anderson Cancer Center for providing editorial support in the preparation of this manuscript.

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