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

QIMING ZHOU[1,2*], FANGFANG ZENG[3*], YAO DING[4], CLIFTON D. FULLER[4] and JIHONG WANG[2]

[1]Department of Oncology, The Sixth People's Hospital, Shenzhen, Guangdong 518052, P.R. China; [2]Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA; [3]Guangdong Provincial Key Laboratory of Food, Nutrition and Health, School of Public Health, Sun Yat-sen University, Guangzhou, Guangdong 510080, P.R. China; [4]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

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

Correspondence to: Professor Jihong Wang, Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, Unit 1420, 1400 Pressler Street, Houston, TX 77030, USA
E-mail: jihong.wang@mdanderson.org

*Contributed equally

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 *et al*	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 *et al*	2016	Italy	Retrospective	NA	NA	30	NA	HNSCC[a]	T1-4N1-3	One radiologist (15 years)	7,000 cGy /33 f	Cisplatin	(11)
Hou *et al*	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 *et al*	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 *et al*	2013	China	Prospective	Consecutive	NA	37	57.0 (45-71)	HNSCC[b]	III-IV	One radiologist (>15 years)	NA	NA	(13)
Nakajo *et al*	2012	Japan	Retrospective	NA	NA	26	65.0 (45-89)	HNSCC[c]	T1-4N0-3	NA	6,000 cGy/30 f	NA	(15)
Hatakenaka *et al*	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 *et al*	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 *et al*	2009	USA	Prospective	NA	NA	33	61.0±10.8	HNSCC[f]	T0-4N1-2bM0	NA	7,040 cGy/32 f	Cisplatin	(7)

[a]Oropharynx, nasopharynx, hypopharynx, larynx, and unknown primary. [b]Oropharynx, hypopharynx, larynx, nasal cavity, oral cavity, and maxillary sinus. [c]Oropharynx, nasopharynx, hypopharynx, larynx, oral cavity and maxillary sinus. [d]Oropharynx, hypopharynx, larynx and oral cavity. [e]Oropharynx, tonsil, base of tongue, supraglottic, glottic and piriform sinus. [f]Larynx, vallecula, tonsil, base of tongue and unknown primary. NA, not available; HNSCC, head and neck squamous cell carcinoma; TN, Taxol + nedaplatin; TNF, Taxol + 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 *et al*	1.5	4,225/106	GE	5	Unknown	128x130	0, 200, 400, 600, 800, 1,000	(10)
Scalco *et al*	1.5	4,500/77	GE	4	260-280	128x128	0, 500, 800	(11)
Hou *et al*	1.5	4,225/106	GE	5	220	128x130	0, 50, 80, 100, 150, 200, 400, 600, 800, 1,000	(12)
Hong *et al*	1.5	Unknown	GE	Unknown	240x240	128x128	0, 800	(14)
King *et al*	1.5	2,000/75	Philips	4	230	112x112	0, 100, 200, 300, 400, 500	(13)
Nakajo *et al*	1.5	6,000/68	Siemens	6	370	112x168	0, 800	(15)
Hatakenaka *et al*	1.5	3,000/73	Philips	3-5	200-230	112x79	0, 300, 1,000	(8)
Vandecaveye *et al*	1.5	7,100/84	Siemens	4	200x250	104x128	0, 50, 100, 500, 750, 1,000	(16)
Kim *et al*	1.5 or 3.0[a]	4,000/89	Siemens	5	260	NA	0, 500, 1,000	(7)

[a]1.5 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.

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

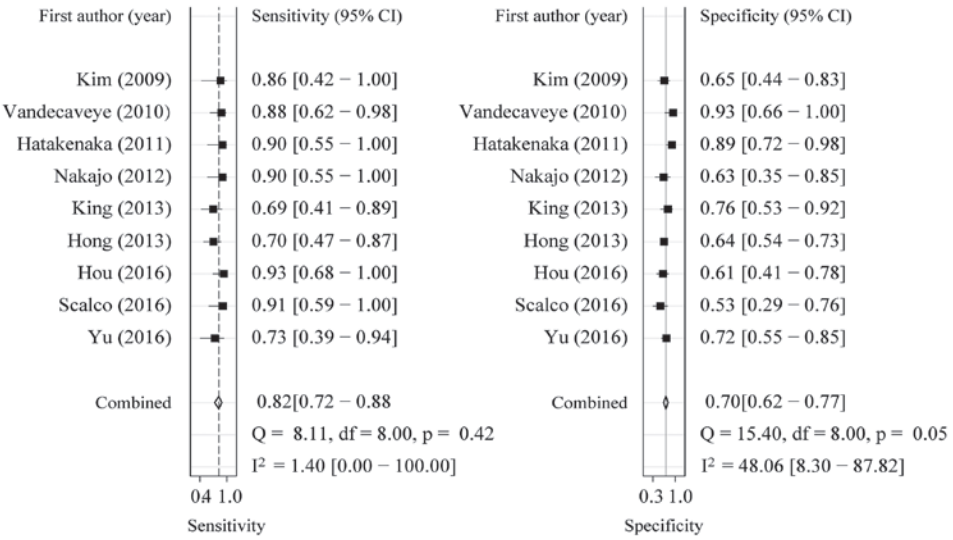

Figure 1. Forest plots of sensitivity and specificity with corresponding 95% confidence intervals for diffusion-weighted imaging to predict locoregional failure of chemoradiotherapy in patients with head and neck squamous cell carcinoma. CI, confidence interval; df, degree of freedom.

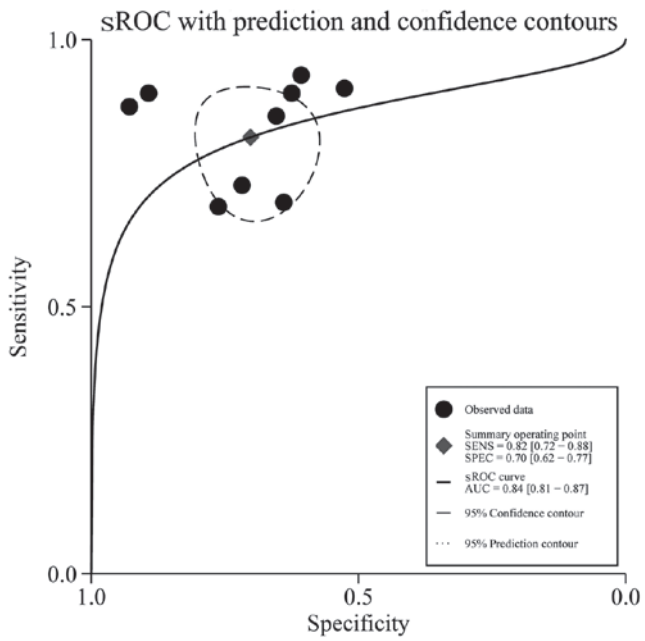

Figure 2. Summary receiver operating characteristic (sROC) curve for all 9 studies. The area under the ROC curve (AUC) of the apparent diffusion coefficient (ADC) was 0.84 (95% confidence interval: 0.81-0.87), indicating good accuracy in predicting locoregional failure of chemoradiotherapy in patients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

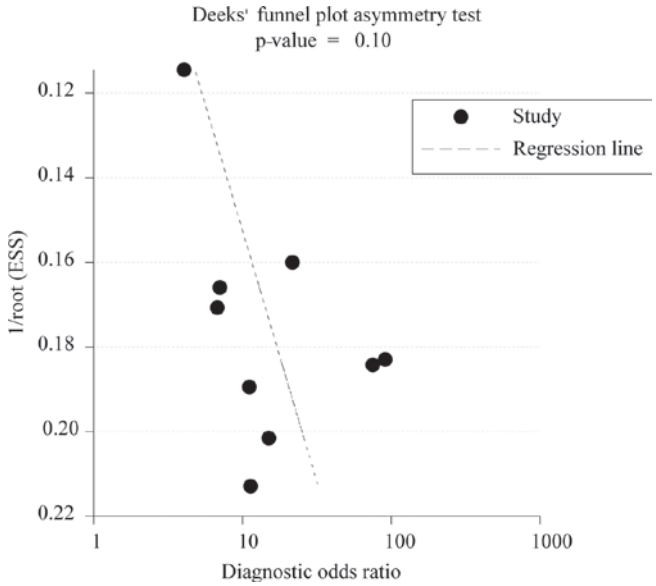

Figure 3. Results of Deeks' funnel plot from the asymmetry test for publication bias. The non-significant slope indicates that no significant bias was observed. ESS, effective sample size.

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 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 intratreatment 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 overestimation 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.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E and Forman D: Global cancer statistics. CA Cancer J Clin 61: 69-90, 2011.
2. King AD and Thoeny HC: Functional MRI for the prediction of treatment response in head and neck squamous cell carcinoma: Potential and limitations. Cancer Imaging 16: 23, 2016.
3. Wu LM, Zhu J, Hu J, Yin Y, Gu HY, Hua J, Chen J and Xu JR: Is there a benefit in using magnetic resonance imaging in the prediction of preoperative neoadjuvant therapy response in locally advanced rectal cancer? Int J Colorectal Dis 28: 1225-1238, 2013.
4. Weis JA, Miga MI, Arlinghaus LR, Li X, Abramson V, Chakravarthy AB, Pendyala P and Yankeelov TE: Predicting the response of breast cancer to neoadjuvant therapy using a mechanically coupled reaction-diffusion model. Cancer Res 75: 4697-4707, 2015.
5. Yoo RE, Choi SH, Kim TM, Lee SH, Park CK, Park SH, Kim IH, Yun TJ, Kim JH and Sohn CH: Independent poor prognostic factors for true progression after radiation therapy and concomitant temozolomide in patients with glioblastoma: Subependymal enhancement and low ADC value. AJNR Am J Neuroradiol 36: 1846-1852, 2015.
6. Padhani AR, Liu G, Koh DM, Chenevert TL, Thoeny HC, Takahara T, Dzik-Jurasz A, Ross BD, Van Cauteren M, Collins D, *et al*: Diffusion-weighted magnetic resonance imaging as a cancer biomarker: Consensus and recommendations. Neoplasia 11: 102-125, 2009.
7. Kim S, Loevner L, Quon H, Sherman E, Weinstein G, Kilger A and Poptani H: Diffusion-weighted magnetic resonance imaging for predicting and detecting early response to chemoradiation therapy of squamous cell carcinomas of the head and neck. Clin Cancer Res 15: 986-994, 2009.
8. Hatakenaka M, Nakamura K, Yabuuchi H, Shioyama Y, Matsuo Y, Ohnishi K, Sunami S, Kamitani T, Setoguchi T, Yoshiura T, *et al*: Pretreatment apparent diffusion coefficient of the primary lesion correlates with local failure in head-and-neck cancer treated with chemoradiotherapy or radiotherapy. Int J Radiat Oncol Biol Phys 81: 339-345, 2011.
9. Matoba M, Tuji H, Shimode Y, Toyoda I, Kuginuki Y, Miwa K and Tonami H: Fractional change in apparent diffusion coefficient as an imaging biomarker for predicting treatment response in head and neck cancer treated with chemoradiotherapy. AJNR Am J Neuroradiol 35: 379-385, 2014.
10. Xiao-ping Y, Jing H, Fei-ping L, Yin H, Qiang L, Lanlan W and Wei W: Intravoxel incoherent motion MRI for predicting early response to induction chemotherapy and chemoradiotherapy in patients with nasopharyngeal carcinoma. J Magn Reson Imaging 43: 1179-1190, 2016.
11. Scalco E, Marzi S, Sanguineti G, Vidiri A and Rizzo G: Characterization of cervical lymph-nodes using a multi-parametric and multi-modal approach for an early prediction of tumor response to chemo-radiotherapy. Phys Med 32: 1672-1680, 2016.

12. Hou J, Yu X, Hu Y, Li F, Xiang W, Wang L, Wang H, Lu Q, Zhang Z and Zeng W: Value of intravoxel incoherent motion and dynamic contrast-enhanced MRI for predicting the early and short-term responses to chemoradiotherapy in nasopharyngeal carcinoma. Medicine (Baltimore) 95: e4320, 2016.
13. King AD, Chow KK, Yu KH, Mo FK, Yeung DK, Yuan J, Bhatia KS, Vlantis AC and Ahuja AT: Head and neck squamous cell carcinoma: Diagnostic performance of diffusion-weighted MR imaging for the prediction of treatment response. Radiology 266: 531-538, 2013.
14. Hong J, Yao Y, Zhang Y, Tang T, Zhang H, Bao D, Chen Y and Pan J: Value of magnetic resonance diffusion-weighted imaging for the prediction of radiosensitivity in nasopharyngeal carcinoma. Otolaryngol Head Neck Surg 149: 707-713, 2013.
15. Nakajo M, Nakajo M, Kajiya Y, Tani A, Kamiyama T, Yonekura R, Fukukura Y, Matsuzaki T, Nishimoto K, Nomoto M and Koriyama C: FDG PET/CT and diffusion-weighted imaging of head and neck squamous cell carcinoma: Comparison of prognostic significance between primary tumor standardized uptake value and apparent diffusion coefficient. Clin Nucl Med 37: 475-480, 2012.
16. Vandecaveye V, Dirix P, De Keyzer F, de Beeck KO, Vander Poorten V, Roebben I, Nuyts S and Hermans R: Predictive value of diffusion-weighted magnetic resonance imaging during chemoradiotherapy for head and neck squamous cell carcinoma. Eur Radiol 20: 1703-1714, 2010.
17. Jones CM and Athanasiou T: Summary receiver operating characteristic curve analysis techniques in the evaluation of diagnostic tests. Ann Thorac Surg 79: 16-20, 2005.
18. Hamstra DA, Lee KC, Moffat BA, Chenevert TL, Rehemtulla A and Ross BD: Diffusion magnetic resonance imaging: An imaging treatment response biomarker to chemoradiotherapy in a mouse model of squamous cell cancer of the head and neck. Transl Oncol 1: 187-194, 2008.
19. King AD, Mo FK, Yu KH, Yeung DK, Zhou H, Bhatia KS, Tse GM, Vlantis AC, Wong JK and Ahuja AT: Squamous cell carcinoma of the head and neck: Diffusion-weighted MR imaging for prediction and monitoring of treatment response. Eur Radiol 20: 2213-2220, 2010.
20. Driessen JP, Caldas-Magalhaes J, Janssen LM, Pameijer FA, Kooij N, Terhaard CH, Grolman W and Philippens ME: Diffusion-weighted MR imaging in laryngeal and hypopharyngeal carcinoma: Association between apparent diffusion coefficient and histologic findings. Radiology 272: 456-463, 2014.
21. Chawla S, Kim S, Dougherty L, Wang S, Loevner LA, Quon H and Poptani H: Pretreatment diffusion-weighted and dynamic contrast-enhanced MRI for prediction of local treatment response in squamous cell carcinomas of the head and neck. AJR Am J Roentgenol 200: 35-43, 2013.
22. King AD, Yeung DK, Yu KH, Mo FK, Bhatia KS, Tse GM, Vlantis AC, Wong JK, Hu CW and Ahuja AT: Pretreatment and early intratreatment prediction of clinicopathologic response of head and neck cancer to chemoradiotherapy using 1H-MRS. J Magn Reson Imaging 32: 199-203, 2010.
23. Wichmann G, Krüger A, Boehm A, Kolb M, Hofer M, Fischer M, Müller S, Purz S, Stumpp P, Sabri O, *et al*: Induction chemotherapy followed by radiotherapy for larynx preservation in advanced laryngeal and hypopharyngeal cancer: Outcome prediction after one cycle induction chemotherapy by a score based on clinical evaluation, computed tomography-based volumetry and (18) F-FDG-PET/CT. Eur J Cancer 72: 144-155, 2017.
24. Brazzelli M, Sandercock PA, Chappell FM, Celani MG, Righetti E, Arestis N, Wardlaw JM and Deeks JJ: Magnetic resonance imaging versus computed tomography for detection of acute vascular lesions in patients presenting with stroke symptoms. Cochrane Database Syst Rev 4: CD007424, 2009.
25. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, Westra WH, Chung CH, Jordan RC, Lu C, *et al*: Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 363: 24-35, 2010.
26. Adelstein DJ and Rodriguez CP: Human papillomavirus: Changing paradigms in oropharyngeal cancer. Curr Oncol Rep 12: 115-120, 2010.
27. Yom SS: NRG-HN002: A randomized phase ii trial for patients with p16 positive, non-smoking associated, locoregionally advanced oropharyngeal cancer, NCT02254278, 2014. https://www.crcwm.org/Attachments/NRG%20HN002%20FastFacts.pdf. Accessed June 20, 2016.
28. Michael A, Boss TLC, Mark A, Rose Edward F, Jackson, *et al*: QIBA PDF MRI technical committee: Activities in diffusion MRI, 2014. https://qibawiki.rsna.org/images/b/bc/QIBA_PDF_DWI_Poster_2014_v1_0.pdf. Accessed May 24, 2014.