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ORIGINAL RESEARCH

Apparent Diffusion Coefficient Calculated with Relatively High b-Values Correlates with Local Failure of Head and Neck Squamous Cell Carcinoma Treated with Radiotherapy

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BACKGROUND AND PURPOSE: Few studies have investigated the relationship between ADC and clinical outcome in HNSCC. Our hypothesis has that relatively high pretreatment ADC would correlate with local failure of HNSCC treated with radiation therapy.

MATERIALS AND METHODS: This includes prospective and validation studies. Seventeen patients treated with radiation therapy for primary HNSCC completed the prospective study. Variables considered to affect local failure including MR imaging–related parameters such as ADC and its change ratio were compared between patients with local failure and controls, and those showing difference or association with local failure were further tested by survival analysis. Furthermore, variables were analyzed in 40 patients enrolled in the validation study.

RESULTS: Relatively high ADC calculated with b-values (300, 500, 750, and 1000 s/mm^2) before treatment, high ADC increase ratio, and treatment method (chemoradiotherapy versus radiation therapy alone) revealed significant difference between patients with local failure and controls or association with local failure. In Cox proportional hazard testing, high ADC before treatment alone showed significant association with local failure (P = .0186). In the validation study, tumor volume before treatment, high ADC before treatment, T stage (T12 versus T34), and treatment method showed significance. Tumor volume before treatment (P = .0217) and high ADC before treatment (P = .0001) revealed significant association with local failure in Cox proportional hazard testing. High ADC before treatment was superior to tumor volume before treatment regarding association with local failure.

CONCLUSIONS: These results suggest pretreatment ADC obtained at high b-values as well as tumor volume correlate with local failure of HNSCC treated with radiation therapy.

ABBREVIATIONS: ADC = apparent diffusion coefficient; AUC = area under the curve; DWI = diffusion-weighted imaging; GTV = gross tumor volume; HNSCC = head and neck squamous cell carcinoma; NPV = negative predictive value; PPV = positive predictive value; ROC = receiver operating characteristic; ROI = region of interest; SI = signal intensity.

The self-diffusion of cell water is affected by temperature and viscosity as well as by barrier structures such as cell membranes[1,2]; thus, DWI reflects microstructural information about tissues. However, it is difficult to evaluate in vivo the relation between diffusive parameters and tissue microstructure without changing other factors, such as temperature and viscosity, which would affect proton diffusion. We have shown that changes in tissue microstructure directly affect the proton diffusion parameters.[3,4] Based on the concept that the ADC reflects the tissue microstructure, the ADC has been used to differentiate malignant from benign conditions: malignancies have been reported to show lower ADC than benign lesions, owing to the high cellularity of the former.[5-9]

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Recent studies have successfully used ADC to predict treatment response, revealing that pretreatment ADC correlates with treatment response[10-13] and that the changes in ADC at an early treatment phase also can predict treatment response.[14-18] Although chemoradiotherapy is a good approach for the treatment of HNSCC because it minimizes functional and social losses arising from surgery such as eating and/or speech impairment and cosmetic problems, there have been few studies about the usefulness of ADC as a surrogate marker of treatment response of HNSCC.[19-23] Furthermore, the method of calculating ADC remains controversial, and it is also still not clear whether pretreatment ADC or ADC change at the early treatment phase is more practical for predicting treatment response.

We hypothesized that pretreatment ADC calculated with relatively high b-values would correlate with local failure of HNSCC treated with radiation therapy.

Materials and Methods

This study included a prospective pilot study to determine clinical and imaging variables related to local failure and a validation study to confirm the results of the prospective study; both were approved by the Committee on Clinical Study at our institution. Some patients

analyzed in the present study overlapped with those of our previous study[23]; however, the variables and methods used for analysis are different.

Patients

Informed consent was obtained from each participant for the prospective study. We enrolled 32 patients who were histologically proved to have primary HNSCC in our institute between April 2006 and July 2008 and who were scheduled to receive radical radiation therapy (>60 Gy to GTV). Patients with a diagnosis of nasopharyngeal cancer were not enrolled because the characteristics of nasopharyngeal cancer are different from those of other types of HNSCC. Nasopharyngeal cancer is known to be more radiosensitive than other types of HNSCC.[24] Among the 32 patients enrolled, 3 were excluded because detection of the primary lesion on DWI was difficult due to small lesions or artifacts, 7 were excluded because early-phase MR imaging could not be obtained or the lesion could not be detected clearly on the early-phase imaging, and 5 were excluded because the radiation dose to the GTV was <60 Gy due to poor patient condition or severe side effects. Therefore, 17 patients (15 men; age range, 37–85 years; median age, 64 years; 7 oropharynx, 8 hypopharynx, 1 larynx, 1 oral cavity) who received radiation therapy with a radiation dose to GTV >60 Gy (range, 64–71 Gy, median, 65.4 Gy) and who had MR images both before treatment and at the early phase of treatment were studied. No patient had a history of receiving chemotherapy or radiation therapy.

For the validation study, 40 patients in total (37 men; age range, 37–85 years; median age, 64 years; 15 oropharynx, 19 hypopharynx, 4 larynx, 2 oral cavity) who had received radiation therapy with a radiation dose to GTV >60 Gy (range, 64–71 Gy; median, 65.4 Gy) between April 2006 and June 2009 and had pretreatment MR imaging including DWI were retrospectively studied. They included 17 patients in the prospective study, 5 of the 7 patients who were excluded from the prospective study because of the lack in MR imaging at an early phase of treatment or the difficulty of detecting lesions on early-phase MR imaging (the remaining 2 patients were not included because they showed local control but the follow-up period was <10 months), and an additional 18 patients who were not enrolled in the prospective study. Informed consent was waived for the retrospective study. No patient had a history of receiving chemotherapy or radiation therapy.

Treatment and Follow-Up

External radiation therapy was performed with 4- or 6-MV x-ray in 1.8–2.0-Gy fractions at 5 fractions per week by using a 3D conformal technique. In the prospective study, concurrent chemoradiotherapy (TS-1 [Tahio Pharmaceutical, Tokyo, Japan] dose of 65 mg/m^2 for 4 weeks followed by 2 weeks of rest while receiving radiation therapy) was given to 13 patients, and the remaining 4 patients were treated with radiation therapy alone due to their condition. TS-1 contains tegafur, gimeracil (5-chloro-2,4-dihydrogenase), and potassium oxonate at a molar ration of 1:0.4:1. In the validation study, concurrent chemoradiotherapy was performed for 35 patients (TS-1 for 32 patients and cisplatin for 3 patients, 5 mg/m^2 for 5 days a week while receiving radiation therapy) and the remaining 5 patients were treated with radiation therapy alone due to their condition. The overall treatment time was defined as the number of days from the start of treatment to the end of treatment.

Patients were followed up for the evaluation of local control. The follow-up evaluation included physical, endoscopic, and radiologic examinations. Contrast-enhanced CT was the base of the radiologic examination, and MR imaging and/or fluorodeoxyglucose–positron-emission tomography/CT were obtained when otorhinolaryngologists considered these examinations were necessary. Histologically confirmed local recurrences during follow-up were considered as local failure. The follow-up period was designated as the total time of follow-up starting at treatment initiation and ending either at histologically confirmed local failure or at last patient contact without local failure. As for the prospective study, 8 patients developed local failure and the remaining 9 patients showed local control during the follow-up period. The follow-up time of patients with local failure ranged from 2.1 to 15.8 months, with a median of 4.6 months. That of patients with local control ranged from 10.5 to 42.7 months, with a median of 23.6 months. All cases but 1 showed local recurrence within 8 months of follow-up; thus, we considered those showing no local recurrence after >10 months of follow-up as local control. As a salvage therapy for lymph node recurrence in patients with local control, transarterial infusion of cisplatin was performed in 1 case.

For the validation study, 13 patients developed local failure, and the remaining 27 showed local control during the follow-up period. The follow-up time of patients with local failure ranged from 2.1 to 17.5 months, with a median of 4.9 months. That of patients with local control ranged from 10.5 to 42.7 months, with a median of 16.4 months. As a salvage therapy for lymph node recurrence in patients with local control, lymph node dissection was performed in 3 cases and transarterial infusion of cisplatin was performed in 2 cases.

MR Imaging

MR imaging was performed by using a 1.5T system (Intera Achieva; Philips Medical Systems, Best, the Netherlands) before the initiation of treatment for both prospective and validation studies, with a maximum gradient strength of 66 mT/m, and a maximum slew rate of 160 mT/m/ms. MR imaging at an early phase of treatment also was performed for the prospective study. The FOV was 200–230 mm with a section thickness of 3–5 mm and a section gap of 0.5–1.5 mm, and a neurovascular coil with sensitivity encoding was used. The subjects were placed in a supine position. Pretreatment images were obtained at a median of 8 days before the start of radiation therapy for both prospective and validation studies. Early treatment-phase images were obtained a median of 7 days after the start of radiation therapy, with a median radiation dose of 10.8 Gy.

In the prospective study, T2-weighted turbo spin-echo, T1-weighted, diffusion-weighted, T2-calculated, and gadolinium-enhanced T1-weighted transverse images of the neck were obtained at pretreatment imaging, and coronal and/or sagittal images also were obtained when needed. For gadolinium-enhanced imaging, gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany), 0.1 mmol/kg body weight, was injected intravenously. In the validation study, the same MR imaging except T2-calculated imaging was obtained for all patients at pretreatment imaging. At early treatment-phase imaging, T2-weighted turbo spin-echo and/or T1-weighted, T2-calculated, and DWIs were obtained.

The imaging parameters for T2-weighted images were as follows: matrix of 512 × 288, turbo factor of 18, TR of 4467 ms, TE of 100 ms, NEX of 2, and examination duration of 2 minutes 27 seconds. The parameters for T1-weighted images were as follows: matrix of 512 × 288, TR of 572–618 ms, TE of 10 ms, NEX of 1, and examination duration of 2 minutes 17–47 seconds. Those for DWIs were as follows: matrix of 256 × 112; TR of 3000 ms; TE of 73 ms; b-factors of 0, 100, 200, 300, 500, 750, and 1000 s/mm^2; δ of 26.08 ms; Δ of 35.96 ms;

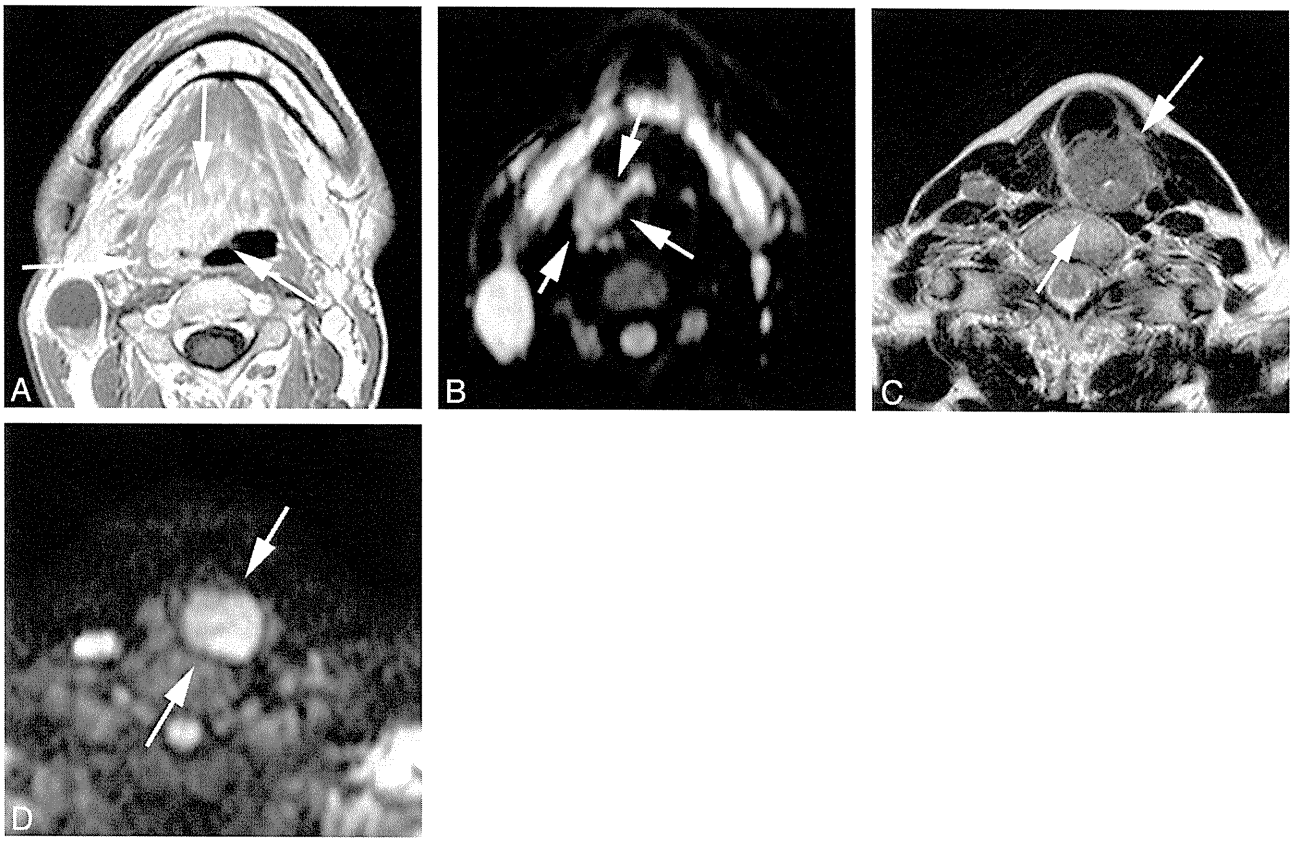

Fig 1. Representative images of local control and failure cases obtained before treatment. *A* and *B*, Transverse gadolinium-enhanced T1-weighted and DWI (b = 1000 s/mm^2) of a local-control case (oropharyngeal cancer, 30s, male, T4N2M0, high ADC before treatment = 0.63 × 10^{-3} mm^2/s). *C* and *D*, T2-weighted and DWI (b = 1000 s/mm^2) of a local-failure case (hypopharyngeal cancer, 60s, female, T4N2M0, high ADC before treatment = 0.99 × 10^{-3} mm^2/s). The arrows indicate primary lesions.

band width of 1645.9 Hz/pixel; NEX of 2; and examination duration of 4 minutes 6 seconds. DWI was obtained with a single-shot spin-echo echo-planar imaging sequence by using a spectral presaturation with inversion recovery for fat suppression. The motion-probing gradient pulses were placed along the x-, y-, and z-axes, and we used synthesized images from the 3 images. The imaging parameters for T2-calculated images were as follows: matrix of 256 × 256; TR of 3000 ms; TEs of 20, 40, 60, 80, 100, and 120 ms; NEX of 1; and examination duration of 8 minutes 12 seconds. Representative images are shown in Fig 1.

ADC Calculation

The ROI was designated as the primary lesion at the level of the largest tumor diameter on DWIs of each b-value to cover most of the lesion, while avoiding cystic or necrotic components with reference to T2-weighted, T1-weighted, and/or gadolinium-enhanced images. This procedure was done by consensus between M.H. and Y.M. without information regarding local failure or control (M.H. and Y.M. each have >15 years of experience in diagnostic radiology). The ADC was calculated as follows: The mean SIs of the ROI under various b-values were fitted to the equation $SI = SI_0e^{-bD}$, where SI is the measured SI, SI_0 is SI at b-value of 0, b is the strength of the motion-probing gradient, and D is ADC. An ADC calculated with 4 different b-values of 0, 100, 200, and 300 s/mm^2 was taken as the value of low ADC and that with b-values of 300, 500, 750, and 1000 s/mm^2 as high ADC.

T2 Calculation

The ROI also was designated as the primary lesion at the level of the largest tumor diameter on T2-calculated images of each TE to cover most of the lesion, while avoiding cystic or necrotic components. This procedure also was done by consensus between M.H. and Y.M. The SIs under various TEs were fitted to the equation $SI = SI_0e^{-TE/T2}$, where SI is the measured SI and SI_0 is the SI at TE of 0.

Tumor Volume

The tumor volume was calculated by delineating the tumor contour on gadolinium-enhanced T1-weighted or T2-weighted spin-echo transverse images. This procedure also was carried out by consensus between M.H. and Y.M. without information regarding local failure or control.

Statistics

For the prospective study, the following variables were selected and tested for their correlation with local failure: age, tumor volume before treatment, tumor volume at the early phase of treatment, volume reduction ratio [1 − (tumor volume at the early phase of treatment)/(tumor volume before treatment)], dose, overall treatment time, T2 before treatment, T2 at the early phase of treatment, T2 increase ratio [(T2 at the early phase of treatment)/(T2 before treatment) −1], high ADC and low ADC before treatment, high ADC and low ADC at the early phase of treatment, high ADC and low ADC increase ratio [(high ADC at the early phase of treatment)/(high ADC before treatment) − 1, [(low ADC at the early phase of treatment)/(low ADC before treatment) −1], tumor location (hypopharynx versus other locations), treatment method (chemoradiotherapy versus radiation therapy alone), T stage (T 12 versus T 34), and N stage (N 01 versus N 23). We used t tests to compare age, tumor volume before treatment, tumor volume at the early phase of treatment, volume reduction ratio, dose, overall treatment time, T2 before treatment, T2 at the early

Table 1: Univariate and multivariate survival analyses of the prospective study (n = 17)

Variable	Univariate Analysis (Log Rank Test), P	Multivariate Analysis (Cox Proportional Hazard Test), P
Treatment method (chemoradiotherapy vs radiotherapy)	.0017	NS[a]
High ADC before treatment (≥0.86 vs <0.86)	.0004	.0186
High ADC increase ratio (≥0.25 vs <0.25)	.0022	NS

[a] NS indicates $P \geq .05$.

Table 2: Univariate and multivariate survival analyses of the retrospective validation study (n = 40)

Variable	Univariate Analysis (Log Rank Test), P	Multivariate Analysis (Cox Proportional Hazard Test), P
T stage (T12 vs T34)	.0009	NS
Treatment method (chemoradiotherapy vs radiotherapy)	<.0001	NS
Tumor volume before treatment (≥9000 mm^3 vs <9000)	.0002	.0217
High ADC before treatment (≥0.86 vs <0.86)	<.0001	.0001

[a] NS indicates $P \geq .05$.

phase of treatment, T2 increase ratio, low ADC before treatment, low ADC at the early phase of treatment, low ADC increase ratio, high ADC before treatment, high ADC at the early phase of treatment, and high ADC increase ratio between local control and failure. Fisher exact test was used to analyze the association between local failure and each of tumor location, treatment method, T stage, and N stage. In the univariate analysis, the curves for local control were estimated by using the Kaplan-Meier method, and the log rank test was used to test the difference between curves. The variables showing differences ($P <$ .05) between local failure and control in the t test or those showing associations ($P <$ .05) with local failure in Fisher exact probability test were analyzed. ROC curve analysis for differentiating local failure from local control was performed for high ADC before treatment and the high ADC increase ratio, which showed significant differences in the t test, to identify the optimal threshold for a binary classifier. With each threshold value of hgh ADC before treatment and the high ADC increase ratio obtained from ROC analysis, and with a treatment method that also showed significant association with local failure, a log rank test was performed. The variables showing association ($P <$ .05) in the log rank test were further tested by multivariate analysis by using the Cox proportional hazard test for their association with local failure.

For the validation study, t test and Fisher exact probability test were used to test the clinical and imaging variables described above except those related to early-phase data (eg, high ADC at the early phase of treatment or high ADC increase ratio) or T2-related data because those were not obtained. A log rank test was performed for T treatment method; tumor volume before treatment; and high ADC before treatment, which showed significant association with local failure or significant differences in the t test; to test the correlation with local failure. The threshold values for tumor volume before treatment and high ADC before treatment were determined by using ROC analysis. The variables showing association ($P <$ .05) in the log rank test were further tested by multivariate analysis by using the Cox proportional hazard test for their association with local failure. A 2 × 2 contingency table was produced, and Fisher exact probability test also was applied for tumor volume before treatment and high ADC before treatment. The correlation between tumor volume before treatment and high ADC before treatment was tested with a linear regression test.

Statistical calculations were performed by using statistical analysis software (JMP, version 7.0.1; SAS Institute, Cary, North Carolina; and Prism, version 5.02; GraphPad Software, San Diego, California). P values <.05 were considered statistically significant. Statistical analysis was carried out in consultation with a biostatistician at our institute.

Results

In the prospective study, high ADC before treatment and the high ADC increase ratio revealed significant differences between local control and failure (On-line Table 1). The treatment method also showed a significant association with local failure (On-line Table 1). ROC analyses resulted in threshold values of 0.86×10^{-3} mm^2/s for high ADC before treatment and 0.25 for the high ADC increase ratio. In univariate analysis by using the log rank test, high ADC before treatment (≥0.86×10^{-3} mm^2/s versus <0.86), the high ADC increase ratio (≥0.25 versus <0.25), and the treatment method also showed significant correlation with local failure (Table 1). In multivariate analysis by using the Cox proportional hazard test, only high ADC before treatment revealed a significant correlation with local failure (Table 1).

In the validation study, tumor volume before treatment and high ADC before treatment showed significant differences between local control and failure (On-line Table 2). T stage and treatment method also showed significant correlation (On-line Table 2). ROC analysis resulted in a threshold value of 9000 mm^3 for tumor volume before treatment. A threshold value for high ADC before treatment was also 0.86×10^{-3} mm^2/s, as in the prospective study. In univariate analysis by using the log rank test, tumor volume before treatment (≥9000 mm^3 versus <9000), high ADC before treatment (≥0.86×10^{-3} mm^2/s versus <0.86), T stage, and treatment method also revealed a significant correlation with local failure (Table 2). In multivariate analysis by using the Cox proportional hazard test, tumor volume before treatment and high ADC before treatment showed significant association (Table 2). The local control curves regarding tumor volume before treatment and high ADC before treatment are shown in Fig 2. There was no significant correlation between tumor volume before treatment and high ADC before treatment (Fig 3). ROC analysis for tumor volume before treatment and high ADC before treatment resulted in AUCs of 0.749 and 0.977, respectively. A 2 × 2 contingency table based on a threshold tumor volume before treatment value showed a sensitivity of 0.846, specificity of 0.741, PPV of 0.611, NPV of 0.909, and accuracy of 0.775 (P = .0007, Fisher exact test; odds ratio = 15.7) and that based on a threshold high ADC before treatment value showed a sensitivity of 0.923, specificity of 0.963, PPV of 0.923, NPV of 0.963, and accuracy of 0.95 ($P <$ .0001, Fisher exact test; odds ratio = 312).

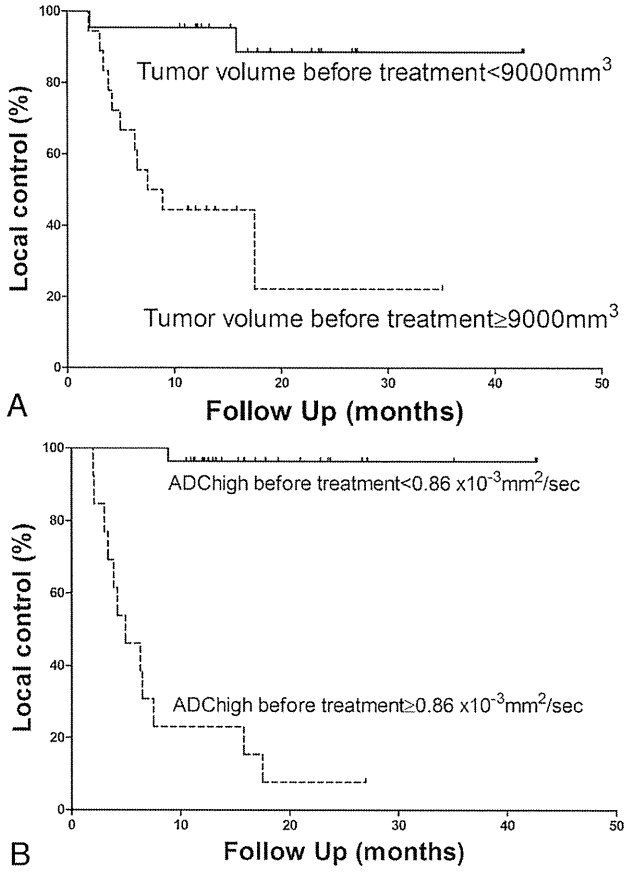

Fig 2. Comparison of local-control curves in the validation study. *A*, Comparison of the local-control curves between tumor volume before treatment <9000 mm^3 (solid line) and ≥9000 mm^3 (dashed line) ($P = .0002$). *B*, Comparison of the local-control curves between high ADC before treatment <0.86 (solid line) and ≥0.86 (dashed line) ($P < .0001$).

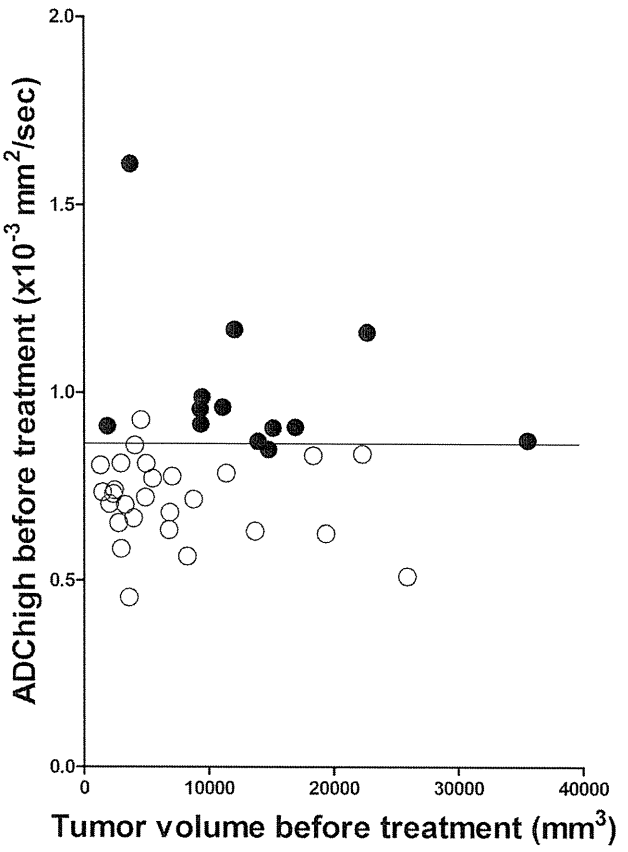

Fig 3. Scatterplot of tumor volume before treatment versus high ADC before treatment. Open and closed circles indicate local control and failure cases, respectively. Horizontal line indicates a threshold value of 0.86 × 10^{-3} mm^2/s for high ADC before treatment.

Discussion

Chemoradiotherapy has been increasingly chosen as a treatment option for advanced HNSCC because it preserves function and minimizes social losses. Therefore, it is of use to differentiate treatment-resistant cases from treatment-sensitive cases before or at the early phase of treatment. Then, more intensive treatment regimens or other treatment options such as surgery could be considered for the treatment-resistant cases. The results from the prospective study revealed that high ADC before treatment correlates with local failure of HNSCC treated with radiation therapy. According to the results from the prospective study, we considered that early phase MR imaging is not necessary for predicting local failure. Therefore, the inclusion criteria for the validation study were extended to those for whom early-phase MR imaging was not obtained. The results of the validation study indicated that high ADC before treatment along with tumor volume before treatment correlates with local failure in HNSCC treated with radiation therapy. We considered that high ADC before treatment would be a superior predictor for local failure based on the results from multivariate analysis and a 2 × 2 contingency table. The slight difference of the results between the prospective and validation studies was probably due to differences in the distributions of tumor volume and T stage. In the prospective study, patients with relatively small lesions were excluded because the lesion could not be detected clearly on an early-phase DWI, as described in the Patients section.

The result that the pretreatment ADC of the primary lesion in HNSCC correlates with local failure is in general consistent with the findings of previous reports, including ours. Kato et al[19] reported that pretreatment ADC showed a weak inverse correlation with tumor regression rates in 28 cases. They evaluated the tumor regression rates based on either CT or MR imaging performed within 2 weeks after finishing chemotherapy and/or radiation therapy, with a median dose of 30 Gy (range, 20–40 Gy) according to the response evaluation criteria in solid tumors. We consider that local failure or control with >6 months of follow-up duration would be more important for managing patients. In contrast, King et al[22] reported that pretreatment ADC was not associated with local failure in a study analyzing 50 cases of HNSCC. We attribute these differences in results to the following. The studies used different methods for calculating ADC. King et al[22] calculated ADC with b-values of 0, 100, 200, 300, 400, and 500 s/mm^2. Low ADC calculated with b-values of 0, 100, 200, and 300 s/mm^2 also resulted in a lack of correlation with local failure in our study. We consider that ADC calculated with relatively high b-values would be appropriate for predicting treatment response because ADC calculated with relatively low b-values is strongly affected by perfusion.[25,26]

The result that the ADC increase ratio at the early phase of treatment correlated with local failure is consistent with that of previous reports. Vandecaveye et al[21] reported that ADC changes at 2 and 4 weeks after initiation of chemoradiotherapy or radiation therapy were correlated with locoregional failure

in a study with 30 HNSCCs, revealing that the cases with a high ADC increase ratio showed locoregional control. As for regional control, Kim et al[20] also reported that a low pretreatment ADC of nodes and a high increase ratio of the ADC of nodes at 1 week after treatment initiation predicted regional control in a study with 33 HNSCCs. Finally, in an experimental study by using a mouse model of squamous cell carcinoma, Hamstra et al[27] reported that a group treated with chemoradiotherapy showed better prognoses, and demonstrated a significant increase in ADC.

In the present study, tumor volume change at the early phase of treatment did not correlate with local failure. Vandecaveye et al[21] reported that the prediction of locoregional failure by using volume change at 2 or 4 weeks after initiation of treatment was inferior to that by using ADC change. The timing of MR imaging in the present study, a median of 7 days after the initiation of treatment and a median of 10.8 Gy, might have been too early to detect a correlation.

As for the accuracy of the clinical outcome prediction, Vandecaveye et al[21] reported that the prediction of locoregional control by using ADC change at 2 weeks after initiation of chemoradiotherapy resulted in an AUC of 0.94, with 88% sensitivity, 91% specificity, 78% PPV, 96% NPV, and 90% accuracy and that using ADC change at 4 weeks resulted in an AUC of 0.97, with 100% sensitivity, 91% specificity, 80% PPV, 100% NPV, and 94% accuracy in a study with 33 cases. King et al[22] reported that the prediction of locoregional control by using the ADC change pattern resulted in 80% sensitivity, 100% specificity, 100% PPV, 83% NPV, and 90% accuracy in a study with 20 cases showing residual masses. As described in the Results section, our present findings in a retrospective validation study with 40 cases were comparable to theirs (AUC of 0.977, 92.3% sensitivity, 96.3% specificity, 92.3% PPV, 96.3% NPV, and 95% accuracy). The advantages of using pretreatment ADC to predict treatment response are as follows: 1) the prediction would be completed before the initiation of treatment, 2) additional MR examinations would not be necessary, and 3) patients with relatively small primary lesions would not be excluded.

There have been studies investigating the relation between MR imaging findings other than the ADC and treatment response in HNSCC.[28,29] Enhanced MR imaging requires contrast material that may elicit side effects, require additional expense, and be inapplicable to patients with severe renal dysfunction. We therefore consider that the prediction of local failure by using pretreatment ADC would be superior.

A limitation of this study is that the total number of patients analyzed was small. A prospective study with a larger number of patients may be needed to confirm the results.

Conclusions

Our study suggests that ADC calculated with relatively high b-values (300, 500, 750, and 1000 s/mm^2) before treatment, as well as tumor volume before treatment, correlate with local failure of primary HNSCC treated with radiation therapy. More intensive treatment regimens such as dose escalation or other treatment options such as surgical resection may be considered for the patients showing high ADC value before treatment.

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Advanced Maxillary Sinus Cancer Treated with Concurrent Chemoradiotherapy with Intra-Arterial Cisplatin/Docetaxel and Oral S-1: Own Experience and Literature Review

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Key Words
Head and neck cancer · Intra-arterial chemoradiotherapy · Cisplatin · Docetaxel · S-1

Abstract
Intra-arterial (IA) chemotherapy for head and neck cancer is effective and multiple IA concurrent chemoradiation (CCRT) protocols have been reported. However, the role of IA CCRT in the multimodality treatment of head and neck cancer is still controversial. We have treated 5 cases of unresectable T4 maxillary sinus squamous cell carcinoma with IA cisplatin (CDDP) and docetaxel (DOC) and CCRT with oral S-1. We report our experience and the effectiveness and feasibility of this combination as an alternative choice of treatment for inoperable head and neck cancer. The patients received an IA infusion of CDDP (50–70 mg/m^2) and DOC (50–60 mg/m^2) through the femoral artery, followed by CCRT with oral S-1. The IA infusion was repeated up to 3 times and the radiation was dosed at up to 60–70 Gy. Complete response was achieved in 4 patients and partial response in one, giving an overall response rate of 100%. The most common grade 3 or 4 toxicities were anorexia (80%), mucositis (80%) and leukopenia (80%), all of which were manageable. CCRT with IA CDDP/DOC and oral S-1 was effective and tolerated. Although preliminary, the response rate encourages further pursuit and definitive evaluation of this combination for the treatment of inoperable advanced head and neck cancer.

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Introduction

Owing to the development of interventional radiological techniques, intra-arterial (IA) chemotherapy for treating head and neck cancer is nowadays widely used and has been studied and evaluated in many institutions. Protocols combining IA chemotherapy with concurrent radiotherapy demonstrated high organ preservation rates in locally advanced head and neck cancer. Multiple trials, particularly those using high-dose cisplatin (CDDP) (RADPLAT) have been reported to show a high response rate [1, 2]. However, the feasibility and the effectiveness of the RADPLAT protocol are still controversial [3, 4].

Docetaxel (DOC) is commonly used in concurrent chemoradiotherapy (CCRT) for head and neck cancer [5–7]. IA chemotherapy combining DOC and CDDP has also previously been reported to be effective in treating head and neck cancer [8, 9].

S-1 is an oral fluorouracil anticancer agent consisting of tegafur, 5-chloro-2,4 dihydropyridine, which inhibits dihydropyrimidine dehydrogenase enzyme activity, and oteracil (potassium oxonate) as an inhibitor of gastrointestinal side effects [10]. In our institution, CCRT using S-1 and retinyl palmitate has been used for treating head and neck cancer to pursue the possibility of organ preservation [11, 12]. In the present study on treating locally advanced unresectable maxillary sinus cancer, IA infusion of CDDP and DOC was added to the regular CCRT with S-1 to maximize the local effect of the CCRT. The aim of this paper is to describe our experience and the effectiveness and feasibility of the combination of IA CDDP, DOC and CCRT with oral S-1 in the treatment of highly advanced maxillary sinus cancer.

Patients and Methods

Between July 2007 and March 2008, 5 patients (3 men, 2 women) with unresectable T4 squamous cell carcinoma of the maxillary sinus (including one patient refusing radical operation) underwent our IA CCRT protocol. Eligible patients were aged <75 years with a performance status of 0 to 1 (table 1). All patients were fully informed about the treatment protocol and written informed consent was obtained.

IA Chemotherapy

The femoral artery was punctured under local anesthesia by Seldinger's method. The tip of the catheter was threaded into the external carotid artery. Fluorography was performed through a micro-catheter to determine the dominant tumor-supplying vessel with digital angiography. Cone-beam computed tomography was also used during angiography to ascertain the stained area. In cases which had multiple tumor-supplying vessels, the dose of CDDP and DOC was divided according to the stained tumor volume.

IA infusion of CDDP (50–70 mg/m^2) and DOC (50–60 mg/m^2) was administered through the micro-catheter on day 1 (fig. 1). The doses of the agents were determined mainly depending on the patients' residual renal and bone marrow functions. A 5-HT3-receptor antagonist was also given to all patients to reduce nausea/vomiting. For patients who were judged to need multiple courses of chemotherapy, IA infusion was repeated up to 3 times in intervals of 4–6 weeks. Depending on the general conditions of the 5 patients, 2 patients received an IA infusion once, 2 patients twice and one patient 3 times (table 1).

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Radiotherapy with S-1

Three-dimensional conformal radiotherapy was performed to the primary sites and regional cervical lymph node areas through a linear accelerator with a 4-MV X-ray. The start of radiotherapy ranged from day 3 to day 7 depending on the general condition of the patient. Conventional fractionation was used with a daily dose of 1.8–2.0 Gy, 5 times a week up to a total dose of 60–70 Gy (fig. 1). S-1 was concurrently administered to the patients orally twice daily at an initial dose of 65 mg/m^2/day [patients with a body surface area (BSA) >1.5 m^2 received 100 mg/day, patients with 1.25 m^2 < BSA < 1.5 m^2 received 80 mg/day, and patients with a BSA <1.25 m^2 received 50 mg/day]. Patients with renal dysfunction received a 60–80% reduced dose of S-1. Retinyl palmitate (50,000 U/day) was also administered intra-muscularly on each day of radiation as an adjuvant for CCRT. S-1 administration was stopped if grade IV toxicity (leukopenia) due to the IA chemotherapy appeared.

Evaluation of Response and Toxicity

Clinical responses of the CRT were evaluated by inspection, fiberscope examination, CT, and MRI 4 weeks after completion of therapy and FDG-PET was performed 8–10 weeks after completion.

All toxicities due to the protocol were evaluated according to the National Cancer Institute-Common Toxicity Criteria (ver. 4.0).

Results

Clinical Response

Five patients with locally advanced maxillary sinus cancer were treated according to our protocol and were evaluated. All patients required hospitalization for intensive care. Their ages ranged from 37 to 67 years. Four patients were considered to have functionally unresectable disease and 1 patient refused surgery. Histologically, all cases were squamous cell carcinoma. Patients' characteristics and results are listed in table 1. The median follow-up duration was 24 months (range 22–36). Of the 5 patients, 4 had a complete response (fig. 2) and one had a partial response, resulting in an overall response rate of 100%. In one case with partial response in the primary region, systemic chemotherapy was given.

Toxicity (table 2)

Table 2 shows the major adverse events during therapy. The most common grade 3 or 4 toxicities were anorexia, mucositis and leukopenia, all of which were manageable. Treatment was temporarily suspended in 3 cases due to the toxicity (febrile neutropenia); however, all patients recovered within 10 days. There was one case with grade 4 colitis which was suspected to be a side effect of DOC and S-1.

Discussion

IA chemotherapy has been reported to be suitable for head and neck cancer therapy because of its easy access to the arterial system. Multiple IA chemoradiation protocols have been reported for head and neck cancer treatment, among which RADPLAT has

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been studied most widely [1, 2]. Robbins et al. [2] reported the feasibility and the effectiveness of the RADPLAT protocol in a multi-institutional setting. However, in 2010, Rasch et al. [3] reported that RADPLAT was not superior to intravenous chemoradiation for advanced head and neck cancer patients regarding locoregional control and survival. The effectiveness of IA chemoradiation in the treatment of locally advanced head and neck cancer is still controversial.

For patients who have unresectable (T4b) disease or who refuse to receive radical operation, CCRT is the current standard therapy. However, it is still difficult to control highly advanced disease by conventional intravenous CCRT protocols. IA infusion allows exposure of the tumor tissue to a high concentration of chemotherapeutic agents. The effectiveness of chemoradiation for highly advanced locoregional disease is maximized if IA CCRT protocols are used in an appropriate patient setting.

Our IA chemoradiation protocol using IA infusion of DOC and CDDP and oral S-1 revealed a high locoregional effect in patients with unresectable head and neck cancer. The combination of DOC and CDDP has been applied to the treatment of multiple cancer types including head and neck cancer [9, 13]. The advantage of this regimen is that the combination of DOC and CDDP has a synergistic anti-cancer effect of the G_2 cell cycle arrest caused by DOC and the G_1 cell cycle arrest caused by CDDP. DOC has also been reported to enhance the cytotoxicity of CDDP to cancer cells by modifying intracellular platinum metabolism [14]. Using a regular dose of CDDP instead of a single high dose, neutralization of the systemic flow of the agents, which is needed in the RADPLAT protocol, becomes superfluous. Additionally, a systemic effect targeting subclinical metastasis can be expected.

Grade 3–4 acute toxicity was observed in 80% of the patients. The incidence of leukopenia and mucositis was high and therefore careful management is necessary. Although not so frequent, colitis due to DOC infusion is an important side effect which should be noted. Kreis et al. [15] first reported on neutropenic enterocolitis. With the combination with S-1, which is another enterotoxic agent, gastroenterological toxicities should be meticulously observed.

Since the report by Rasch et al. [3], the efficacy of IA chemoradiation for head and neck cancer has been questioned. However, we believe that if technical procedures and protocols are improved, IA CCRT is still an effective method for a certain group of patients. Although feasibility was proved, the incidence of toxic events, mainly hematologic, was high and our protocol may not be suitable as a standard therapy. However, the response rate encourages further pursuit and definitive evaluation of this combination for treating locally highly advanced unresectable head and neck malignancies.

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Table 1. Patients' characteristics and results

Patient No.	Age/ gender	T	N	IA infusions (n)	Results	Treatment followed	Survival period	Alive at present
1	45/F	4b	2b	3	CR		36 months	yes
2	67/M	4a	2b	2	PR	chemotherapy	27 months	unknown
3	37/M	4b	0	1	CR		26 months	yes
4	62/M	4b	2b	2	CR		22 months	yes
5	61/F	4a	0	1	CR		22 months	yes

Table 2. Incidence of major acute toxicity (≥grade 3)

Mucositis	4 (80%)
Leukopenia	4 (80%)
Nausea/vomiting	1 (20%)
Diarrhea	1 (20%)
Anorexia	3 (60%)

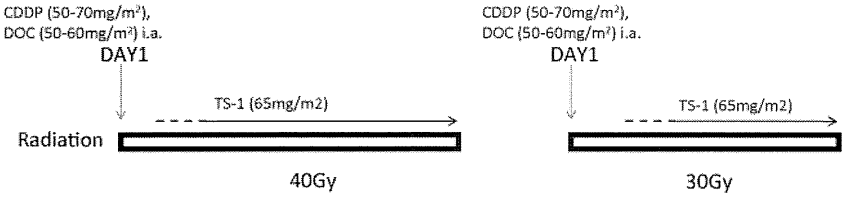

Fig. 1. Treatment schedule for chemoradiotherapy using IA infusion.

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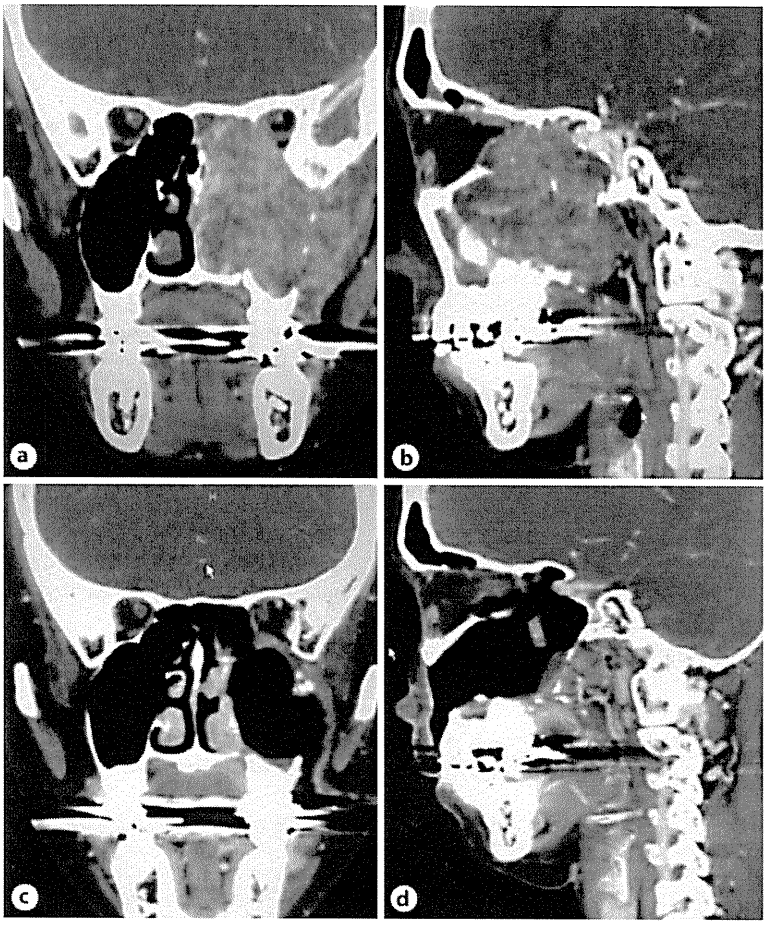

Fig. 2. Squamous cell carcinoma of the left maxillary sinus (case No. 1: T4aN0M0). Enhanced CT scan (**a** coronal view; **b** sagittal view) shows a tumor in the left maxillary sinus extending to the orbital apex. After treatment, clinical CR was obtained (**c** coronal view; **b** sagittal view).

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