放射線治療

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abstract

乳癌診療における放射線治療は，乳癌診療のなかで適応される頻度の高い治療方法である．特に原発性乳癌では，乳房温存療法の普及に伴って，多くの症例が放射線治療を施行される．これまで，乳房温存術後の放射線治療は全乳房に照射することが標準的であったが，リンパ節転移陽性の高リスク患者に対しては鎖骨上窩への照射も勧められている．一方，欧米では低リスク患者での加速乳房部分照射が普及しつつあり，全乳房照射とのランダム化比較試験（RCT）の結果が待たれるところである．また高齢患者での照射省略や短期照射の安全性についてもRCTの結果が示されている．乳房温存療法では欧米のエビデンスが浸透してきたが，一方，乳房切除後放射線治療については，わが国における施行率は十分とはいえない．わが国において，どのような症例で乳房切除後放射線治療が必要なのかについてはまだ議論の余地がある．

I はじめに

乳癌は，ほとんどが腺癌であるが，ほかの臓器原発の腺癌と比べると比較的放射線感受性が高い．乳癌診療のなかでは，乳房温存療法における放射線治療や乳房切除術後の予防照射，進行癌に対する根治的・姑息的照射や術前照射，局所再発や遠隔転移に対する照射など，さまざまな局面において多くの役割を担っている．

また一方，乳癌においては化学療法や内分泌療法などの全身療法が非常に重要である．初発・再発を問わずこれらの治療法と放射線療法をどのように組み合わせ，どのような順序で行うかということは近年大きな関心が寄せられており，症例ごとによく検討されるべきである．

本稿では原発性乳癌に対する放射線治療として，乳房温存療法における放射線治療と乳房切除後放射線治療について概説する．

II 放射線治療の潮流

この約20年間で乳癌治療において放射線治療が用いられる率は飛躍的に増加している．その主たる理由は乳房温存療法の急速な普及である．欧米の大規模な臨床試験を経て，乳房温存療法が早期乳癌の標準治療のひとつとして認知され，乳房温存術後放射線治療の有用性も証明されてきた．わが国においては，当初，放射線治療を行わない乳房温存手術単独での乳房温存の試みも数多くなされた．しかし，欧米のランダム化比較試験（RCT）により放射線治療の有用性が示され，日本乳癌学会の全国統計でも乳房温存術後照射の比率は上昇している（図1）[1]．

一方，乳房切除後の放射線治療は，局所・領域再発を有意に低下させたが，生存率の向上が明確ではなかったため，1970年以降は急速に衰退していった．

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3 術後局所再発に対する放射線治療戦略

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SUMMARY

遠隔転移を伴わない術後局所再発は，積極的な治療により根治可能な場合がある。治療方針の決定には初期治療時に放射線治療が行われたかどうかが重要な因子となる。基本的には手術・放射線治療・全身療法の集学的治療が必要である。すでに照射された領域やその近傍に再照射する場合には，初回治療時の線量分布に留意し，照射線量や照射野の範囲を十分に検討する必要がある。

はじめに

乳癌の局所に限局した再発は，根治を目指した治療戦略を考慮するべきである。一方，遠隔転移を伴う局所再発は，全身的な再発の一部として考えるべきであり，全身療法や緩和療法が主体となる。したがって，この稿では局所に限局した再発に対する治療戦略のみを取り上げる。

乳癌の術後局所再発は，乳房温存手術後と乳房切除後の場合で大きく分けられる。さらにその治療方針は，術後に放射線治療を施行されたかどうかで大きく異なる。この稿では，それぞれの場合について治療戦略を概説する。

I 術後局所再発に対する治療の基本的な戦略

乳癌の術後局所再発の定義は，乳房温存療法後では温存乳房内の再発と領域リンパ節(腋窩・鎖骨上窩・鎖骨下窩・胸骨傍リンパ節)への再発であり，乳房切除術後であれば，胸壁と領域リンパ節への再発である。局所再発は全身的な再発の一部として発症することがあり，CTやMRI，超音波検査や核医学的画像検査などで，全身検索を行うことが重要である。これらの検査にて遠隔転移が否定された場合，遠隔再発に対する治療戦略と異なり，根治を目指した治療を選択するべきである。可能な限り手術療法を考慮し，術後に放射線治療を施行していない場合や，施行していない領域に対しては放射線治療も施行するべきである。また，組織学的所見に基づき，全身療法についても決定する。

NCCN(national comprehenzive cancer network)ガイドラインの指針を図1に示す。

治療の線量については再発部位によって異なるが，照射歴のない症例では広範囲に45～50 Gy/1.8～2.0 Gyの線量を照射し，再発腫瘍床を中心に10～20 Gyのブースト照射を行う。

II 乳房温存療法後の局所再発

局所再発の多くは術後5年以内に生じるが，5年以降での再発をきたすこともある。EBCTCGのメタアナリシスによる10年局所再発率は，初回手術時の腋窩リンパ節転移陰性患者で10%，リン

治療編 局所療法

放射線療法

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SUMMARY

乳癌に対する放射線治療は多岐にわたる。浸潤性乳管癌に対する乳房温存療法は，同側乳房内再発を低下させることがよく知られている。また，2006年に報告されたメタアナリシスの結果では，生存率にも寄与することが示された。非浸潤性乳癌に対する乳房温存療法においては生存率には寄与しないものの，同側乳房内再発を有意に低下させるので推奨されている。乳房切除術後放射線治療は腋窩リンパ節転移4個以上の症例において，適切な全身療法との併用により生存率を向上させる。骨転移に対する放射線治療は疼痛の緩和，骨折や神経症状の予防のために行われる。脳転移に対する放射線治療は頭蓋内圧の亢進や神経症状の緩和に有効である。近年ではラジオサージャリーも普及してきているが，多発性脳転移の場合には全脳照射を優先するべきである。

背景

乳癌に対する放射線治療は，乳房温存療法や乳房切除後の予防照射，進行・再発乳癌に対する照射，骨・脳転移に対する姑息照射など多岐にわたっている。本稿では，それぞれについて一般的に行われている治療法と最近の動向について述べる。

現状

1．乳房温存療法における放射線治療

わが国における乳房温存手術は1980年代から急速に普及し，乳癌学会による癌登録によると，2006年には原発性乳癌に対する手術の約59.3％に至っている。当初は腫瘍周囲を大きく切除し放射線治療が省略される例も多く認められた。しかし2006年では乳房温存術のうち放射線治療が施行された症例は82.3％で，1995年の66.4％と比べると多くの症例で放射線療法が行われるようになった。

1）放射線治療の意義

乳房温存術後の放射線治療は温存乳房内に残存する顕微鏡的残存腫瘍の根絶を目的とする。欧米では放射線治療の必要性を検証する7つのランダム化比較試験が行われ，いずれの試験においても照射群は非照射群に比し有意な乳房内再発の低下が認められた。またEarly Breast Cancer Trialists' Collaborative Group (EBCTCG)より報告された，ランダム化比較試験のメタアナリシスでは，10の臨床試験に登録された7,311症例において，放射線治療を施行した場合に局所再発は70％減少するとしている。また，これまで個々のランダム化比較試験では，放射線治療を行うことで生存率に有意差を認めたものはなかったが，このメタアナリシスでは，15年での死亡の絶対リスクが5.4％減少することが示された(図1)。

2）乳房温存術後の放射線治療は全症例に必要か

一方，照射による有害事象やコストを避けるために術後照射を省略できる群を探る研究もなされている。腫瘍が小さく，手術の切除範囲が大きいほど，また患者年齢が高いほど照射省略の可能性があると考えられるが，Milan Ⅲ試験では扇状部分切除を受けた55歳以上の患者群でも照射が有意に局所再発を抑制した。Harvard Joint Center for Radiation Therapy では局所再発のリスクが最も少ないとされる患者(2cm以下の腫瘍・腋

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G 乳癌

分類

❶ 乳癌の組織分類

わが国では日本乳癌学会の乳癌取扱い規約にもとづいて分類される（表1）。

❷ 乳癌の病期分類

UICC[注1]のTNM病期分類が2009年に改訂され，第7版となった（表2）。日本乳癌学会の乳癌取扱い規約も使用されるが，主にはUICCの分類が用いられる。

表1 乳癌の組織分類（乳癌取扱い規約第16版）

1 非浸潤癌	1a 非浸潤性乳管癌（DCIS） 1b 非浸潤性小葉癌（LCIS）	
2 浸潤癌	2a 浸潤性乳管癌	2a1 乳頭腺管癌 2a2 充実性乳管癌 2a3 硬癌
	2b 特殊型	2b1 粘液癌 2b2 髄様癌 2b3 浸潤性小葉癌 2b4 腺様嚢胞癌 2b5 扁平上皮癌 2b6 紡錘細胞癌 2b7 アポクリン癌 2b8 骨・軟骨化性を伴う癌 2b9 管状癌 2b10 分泌癌（若年性癌） 2b11 浸潤性微小乳頭癌 2b12 基質産生癌 2b13 その他
3 Paget癌		

[注1] UICC，Unio Internationalis Contra Cancrum：国際対がん連合

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CLINICAL INVESTIGATION

ESOPHAGEAL STENOSIS ASSOCIATED WITH TUMOR REGRESSION IN RADIOTHERAPY FOR ESOPHAGEAL CANCER: FREQUENCY AND PREDICTION

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Purpose: To determine clinical factors for predicting the frequency and severity of esophageal stenosis associated with tumor regression in radiotherapy for esophageal cancer.

Methods and Materials: The study group consisted of 109 patients with esophageal cancer of T1–4 and Stage I–III who were treated with definitive radiotherapy and achieved a complete response of their primary lesion at Kyushu University Hospital between January 1998 and December 2007. Esophageal stenosis was evaluated using esophagographic images within 3 months after completion of radiotherapy. We investigated the correlation between esophageal stenosis after radiotherapy and each of the clinical factors with regard to tumors and therapy. For validation of the correlative factors for esophageal stenosis, an artificial neural network was used to predict the esophageal stenotic ratio.

Results: Esophageal stenosis tended to be more severe and more frequent in T3–4 cases than in T1–2 cases. Esophageal stenosis in cases with full circumference involvement tended to be more severe and more frequent than that in cases without full circumference involvement. Increases in wall thickness tended to be associated with increases in esophageal stenosis severity and frequency. In the multivariate analysis, T stage, extent of involved circumference, and wall thickness of the tumor region were significantly correlated to esophageal stenosis ($p = 0.031$, $p < 0.0001$, and $p = 0.0011$, respectively). The esophageal stenotic ratio predicted by the artificial neural network, which learned these three factors, was significantly correlated to the actual observed stenotic ratio, with a correlation coefficient of 0.864 ($p < 0.001$).

Conclusion: Our study suggested that T stage, extent of involved circumference, and esophageal wall thickness of the tumor region were useful to predict the frequency and severity of esophageal stenosis associated with tumor regression in radiotherapy for esophageal cancer. © 2011 Elsevier Inc.

Esophageal stenosis, Radiotherapy, Esophageal cancer, Chemoradiation.

INTRODUCTION

Esophageal cancer continues to have a poor prognosis despite recent improvements in diagnosis and treatment. Surgery has been a standard treatment option for resectable locally advanced esophageal cancer. For early esophageal cancer limited to the mucosal layer, endoscopic mucosal resection has been used as a standard treatment. Radiotherapy, with or without chemotherapy, has been accepted as a treatment for unresectable locally advanced cancer and early cancer not indicated for mucosal resection. However, along with recent improvements in radiation and chemotherapy, some reports have suggested that definitive chemoradiation is a potentially curative treatment for localized esophageal cancer and may achieve the same survival benefit as radical surgery (1–6).

A favorable treatment response can be expected with chemoradiation in a significant proportion of cases of esophageal cancer. However, we often find that stenosis in the tumor region of the esophagus worsens despite tumor regression during the course of radiotherapy. Such "esophageal stenosis" does not result from late toxicity but rather stenotic change experienced concomitant with tumor shrinkage in response to radiotherapy. If the esophageal stenosis worsens, the patients may experience dysphagia and oral intake disorders, which can substantially decrease their quality of life.

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Nonetheless, there have been no studies evaluating the frequency or severity of esophageal stenosis in such cases. Recently, we provided the first preliminary results regarding the frequency of esophageal stenosis associated with tumor regression, and the candidate risk factors for this condition, in 47 esophageal cancer patients treated with radiotherapy (7).

The purpose of this study was to determine and validate the risk factors most useful for predicting the frequency and severity of esophageal stenosis occurring in association with tumor regression in patients receiving radiotherapy for esophageal cancer. We investigated the correlation between esophageal stenosis after radiotherapy and each of the clinical factors with regard to tumors and therapy. For validation of the correlative factors for esophageal stenosis, an artificial neural network (ANN) was used to predict the esophageal stenotic ratio.

METHODS AND MATERIALS

Patients

The study group consisted of 109 patients with esophageal cancer treated with definitive radiotherapy and achieving a complete response (CR) of the primary lesion at Kyushu University Hospital between January 1999 and December 2007. Patient characteristics are shown in Table 1. The median age of these patients was 69 years (range, 42–87 years); 95 were male and 14 female. The data of the 109 patients were used for training an ANN, which is described later.

Table 1. Patient, tumor, and treatment characteristics of 109 patients

Age (y)	69 (42–87)
Gender	
Male	95
Female	14
Pathology	
Squamous cell carcinoma	107
Small cell carcinoma	2
Portion	
Ce	14
Ut	32
Mt	46
Lt	16
Ae	1
T stage	
T1	38
T2	22
T3	30
T4	19
Extent of involved circumference	
Full	33
Not full	76
Tumor length (mm)	40 (10–110)
Wall thickness of tumor region (mm)	7.7 (2–55)
Total radiation dose (Gy)	
<65	32
≥65, <70	68
≥70	9
Concurrent chemotherapy	
Performed	98
Not performed	11

Abbreviations: Ce = cervical esophagus; Ut = upper thoracic esophagus; Mt = middle thoracic esophagus; Lt = lower thoracic esophagus; Ae = abdominal esophagus. Values are number or median (range).

For ANN validation analysis, a different group of 21 esophageal patients achieving CR between January 2008 and December 2009 were analyzed. The characteristics of these patients are shown in Table 2. The median age was 65 years (range, 30–81 years), and all 21 patients were male. Written informed consent was obtained from all patients enrolled in this retrospective study.

Pretreatment evaluation

The extent of disease was evaluated by physical examination, chest radiography, esophagoscopy, barium esophagography, and computed tomography (CT) of the neck, chest, and abdomen in all patients. Bronchoscopy was performed when tracheobronchial involvement was suspected. Endoscopic ultrasound was applied when the transducer could pass through the tumor. Clinical stage was defined according to the criteria of the International Union Against Cancer (1997) (8). The extent of involved circumference and the tumor length were evaluated with esophagography and esophagoscopy, and wall thickness was evaluated with contrasted-enhanced CT images before radiotherapy by measuring the thickness of the thickest portion of the tumor. These characteristics are summarized in Table 1.

Treatments

Radiotherapy was performed using 4-, 6-, or 10-MV external photon beams delivered at a daily dose of 1.8–2 Gy, five times per week with a Clinac 21EX linear accelerator (Varian Medical Systems, Palo Alto, CA). The regional radiotherapy was delivered through anteroposterior portals in a T-shaped field including the bilateral supraclavicular, mediastinal, and abdominal regional lymph nodes or an I-shaped field including the mediastinal and abdominal regional lymph nodes, at a dose of 40–41.4 Gy, and the boost was delivered through parallel or nonparallel opposed oblique portals avoiding the spinal cord using 10-MV photon beams. The total dose ranged from 54 to 71.4 Gy (median, 65 Gy). Total dose over 60 Gy was administered to 104 of 109 patients. Ninety-eight patients were treated with radiation and concurrent chemotherapy, and 11 patients were treated with radiation alone (Table 1). The concurrent chemotherapy consisted of cisplatin (CDDP) or carboplatin plus 5-fluorouracil

Table 2. Patient, tumor, and treatment characteristics of 21 patients for validation analysis

Age (y)	65 (30–81)
Gender	
Male	21
Female	0
T stage	
T1–2	9
T3–4	12
Extent of involved circumference	
Not full	16
Full	5
Tumor length (mm)	50 (20–100)
Wall thickness of tumor region (mm)	13 (3–29)
Radiation total dose (Gy)	
<65	2
≥65, <70	18
≥70	1
Concurrent chemotherapy	
Performed	19
Not performed	2

Values are number or median (range).

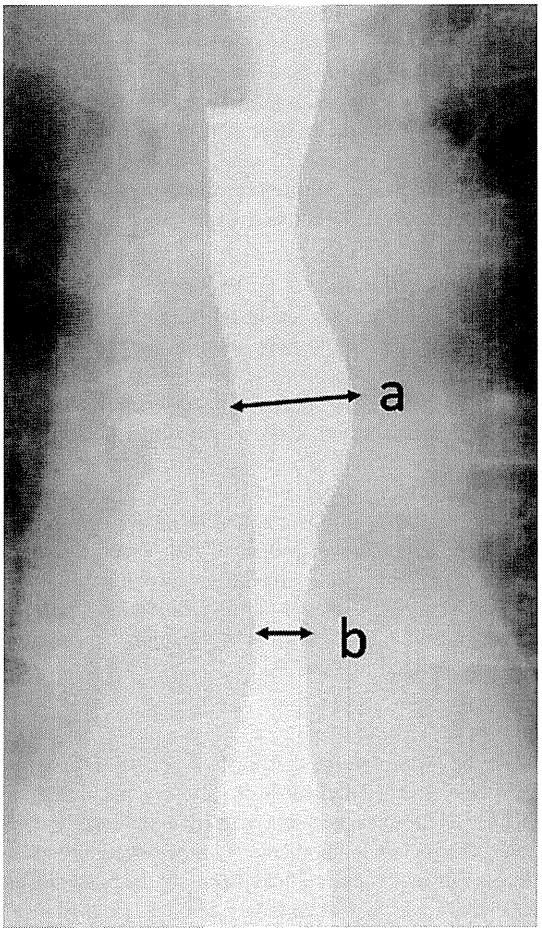

Fig. 1. Esophagography image. We measured the lumen diameter of the narrowest part (b) and the widest part of the oral side (a) of the primary site after radiotherapy. The esophageal stenotic ratio (c) (presented as a percentage) was then calculated as $c = (a - b)/a \times 100$.

(5-FU). The concurrent chemotherapy regimen for most patients consisted of a daily 24-h low-dose protracted infusion of 5 mg/m^2/d of CDDP and 250–300 mg/m^2/d of 5-FU on days when radiotherapy was performed. Any palliative treatments for esophageal stenosis, such as balloon dilatation or insertion of an esophageal stent, were not performed before radiotherapy.

Response evaluation

The response was determined at 1 month after the completion of treatment by using esophagography and esophagoscopy in the majority of patients. In patients with poor general condition at that time, esophagoscopy was used tentatively, and esophagography was performed several weeks later. All examinations were performed within 3 months after the completion of radiotherapy. The response of the primary tumor was evaluated by the criteria of the Japanese Society for Esophageal Diseases, which are based on the findings from esophagograms and esophagoscopy (9). A CR was defined as the complete disappearance of the tumor lesion and ulceration from esophagography and esophagoscopy. A post-treatment biopsy was performed only if clinically indicated.

Evaluation of esophageal stenosis after radiotherapy

Esophageal stenosis was evaluated using the images of esophagography performed for the response evaluation within 3 months after the completion of radiotherapy, as follows. Using the esophagographic image that most clearly demonstrated the stenotic change, we measured the lumen diameter at the widest part (a in Fig. 1) of the oral side and the narrowest part (b in Fig. 1) of the primary site. The stenotic ratio (c; expressed as a percentage) was then calculated as $c = (a - b)/a \times 100$. The four stenotic levels were defined according to stenosis ratio as follows: stenosis Level 1, stenotic ratio of 0–24%; Level 2, 25–49%; Level 3, 50–74%; Level 4, 75–100% (Table 3). Esophageal stenosis is increasing severity from Level 1 to Level 4.

Table 3. Patients according to stenosis levels after treatment

Stenosis level	Stenotic ratio (%)	Patients, *n* (%)
1	0–24	67 (61)
2	25–49	17 (16)
3	50–74	9 (8)
4	75–100	16 (15)

Statistical analysis

Survival rate and local control rate were calculated by the Kaplan-Meier method from the date of initiation of treatment. We estimated the correlation between the esophageal stenosis level after radiotherapy and each of the clinical factors related to the tumors and therapy. For univariate analysis, a χ^2 test was performed to compare the distribution of the characteristics of patients and treatments among the stenosis levels. For multivariate analysis, logistic regression analysis was performed. Differences were considered statistically significant at $p < 0.05$.

Construction of an ANN for prediction of esophageal stenosis ratio associated with tumor regression and its validation

An ANN is one of machine learning classifiers and a computational model simulating neural networks in the human brain. The ANN can learn the relationship between input data and teaching data. In other words, a mathematical model representing the relationship between input data and teaching data can be constructed by changing weighting factors connecting neurons in the ANN in a learning stage. Figure 2 shows an ANN constructed in this study for predicting esophageal stenotic ratio. The ANN has recently been applied to a variety of pattern recognitions and data

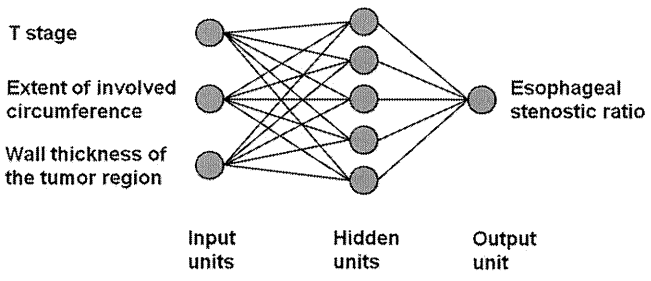

Fig. 2. An artificial neural network for predicting esophageal stenostic ratio, which consisted of three input units, five hidden units, and one output units. Each combination of a circle and a solid line represent a neuron, and the junction between the end of each solid line and the next connecting neuron represents a synapse. The connection weighting factors between neurons can be changed in a learning stage of the artificial neural network, which is similar to changing the synapse strength in learning stage of human being.

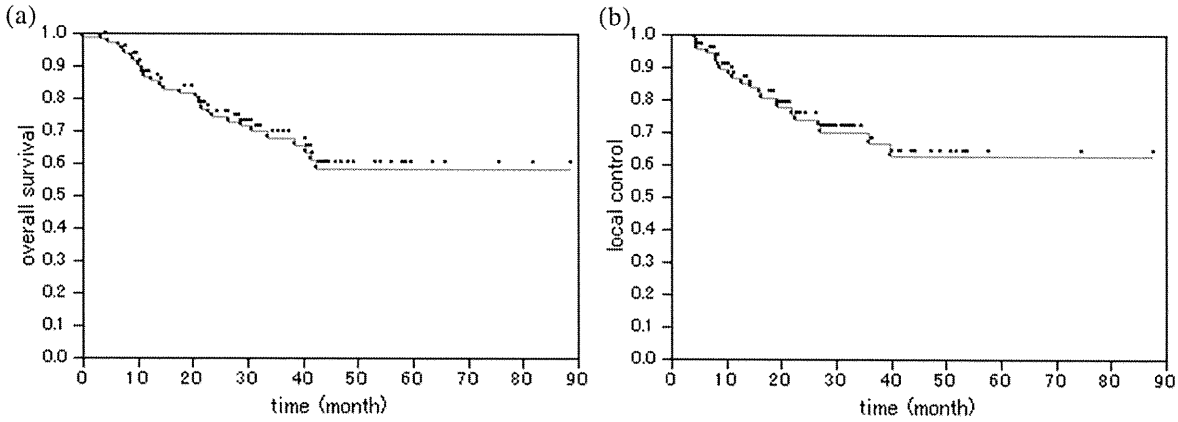

Fig. 3. (a) Overall survival probabilities in 109 patients. (b)Local control probabilities in 109 patients.

classifications (10–13) in the diagnostic field, but there are no trials to predict esophageal stenosis in the radiotherapy field.

For validating the correlative factors for esophageal stenosis found in this study, an ANN was used to predict the esophageal stenotic ratio. If the ANN can learn the relationship between the esophageal stenotic ratio and the selected factors and use this relation to predict the stenotic ratio, then it would be feasible to use the selected factors to directly predict the esophageal stenotic ratio. We trained the ANN and then tested its ability to predict the esophageal stenotic ratio using the three most correlative factors from the multivariate analysis, all of which yielded significant differences. For this purpose, we constructed an ANN with input units for the three prognostic factors, five hidden units, and one output unit corresponding to the predicted value of the stenotic ratio. The hyperbolic tangent (tanh) function was used as a neuron output function. The ANN was trained using 109 patients' data based on a back-propagation algorithm with a learning coefficient of 0.03 until a convergence criterion of 0.01 or the maximum number of iterations (100,000) was reached. The relationship between the predictive value of stenotic ratio and actual stenotic ratio measured by radiation oncologists was examined in 109 patients. In addition, the ANN constructed by the 109 patients was applied to a different group of 21 patients with esophageal cancer treated with definitive radiotherapy and achieving CR between January 2008 and December 2009, and the correlation between the predictive values and actual stenotic ratios was also tested. In this validation test stage for the ANN, the three prognostic factors of 21 patients were input to the ANN trained by the 109 patients, and then the ANN calculated the output according to the same weighting factors in the network as the 109 patients. Finally, the output of the ANN (−1.0 to +1.0) was linearly converted into the esophageal stenostic ratio (0 to 100%). This test procedure can be used for clinical situations.

RESULTS

Of all 109 patients, the median overall survival time was 26 months. The 2-year and 3-year overall survival rates were 74% and 68%, respectively (Fig. 3a). The 2-year and 3-year local control rates were 74% and 66%, respectively (Fig. 3b).

The number and percentage of patients with stenosis at each of the four levels is shown in Table 3. Sixty-seven patients (61%) had Level 1, 17 patients (16%) had Level 2, 9 patients (8%) had Level 3, and 16 patients (15%) had Level 4 stenosis. The correlation between each of the factors evaluated and the proportion of patients with each stenosis level is summarized in Table 4. Stenosis tended to be more severe and more frequent in patients with T3–4 tumors compared with those with T1–2 tumors. The proportions of T1–2 and T3–4 cases with Level 4 stenosis were 3% and 29%, respectively. In regard to the extent of involved circumference, 2% and 43% of the cases, without and with full circumference involvement, had Level 4 stenosis, respectively. The stenosis level in the cases with full circumference involvement tended to be higher than the stenosis level in the cases with less than full circumference involvement. Among cases with a tumor thickness of <10 mm and those with a tumor thickness of ≥10 mm, the proportions of patients with Level 4 stenosis were 2% and 32%, respectively. Increases of wall thickness also tended to be associated with increases in esophageal stenosis severity and frequency.

The results of the statistical analysis are summarized in Table 4. In the univariate analysis, significant differences appeared for T stage, wall thickness of the tumor region, extent of involved circumference, and tumor length ($p \leq 0.005$). In the multivariate analysis, significant differences appeared only for T stage ($p = 0.031$), extent of involved circumference ($p < 0.0001$), and wall thickness of the tumor region ($p = 0.0011$). These three factors significantly correlated with esophageal stenosis were defined as "risk factors," and we estimated the correlation between the number of risk factors and the esophageal stenosis level. This result is shown in Table 5. Depending on the increase in the number of risk factors, the proportion of severe esophageal stenosis tended to be significantly increased. Seventy-nine percent of the patients who had all three risk factors showed Level 3 or greater esophageal stenosis.

Figure 4a shows the relationship between the stenotic ratios predicted by the ANN and the actual stenotic ratio measured by radiation oncologists in 109 patients. The esophageal stenotic ratio predicted by the ANN, which learned three important prognostic factors found using the multivariate analysis (i.e., T stage, extent of involved circumference, and wall thickness of the tumor region) was significantly correlated with the actual observed stenotic ratio,

Table 4. Frequency of each stenosis level according to each factor

Characteristic	Patients (*n*)	Frequency of each stenosis level (%) according to each factor				*p*	
		1	2	3	4	Univariate	Multivariate
Age (y)						0.80	0.96
<70	55	65	13	7	15		
≥70	54	57	19	9	15		
Gender						0.49	0.47
Male	95	62	17	8	13		
Female	14	62	7	7	24		
T stage						<0.0001*	0.031*
T1–2	60	85	10	2	3		
T3-4	49	33	22	16	29		
Extent of involved circumference						<0.0001*	<0.0001*
Not full	76	78	16	4	2		
Full	33	24	15	18	43		
Tumor length (mm)						0.0005*	0.16
<50	59	76	12	5	7		
≥50	50	44	20	12	24		
Wall thickness of tumor region (mm)						<0.0001*	0.0011*
<10	62	84	11	3	2		
≥10	47	32	21	15	32		
Radiation total dose (Gy)						0.58	0.10
<65	32	72	9	6	13		
≥65, <70	68	59	19	9	13		
≥70	9	44	11	11	33		
Concurrent chemotherapy						0.23	0.39
Performed	98	62	17	6	15		
Not performed	11	55	9	27	9		

* $p < 0.05$.

with a correlation coefficient of 0.864 ($p < 0.001$). Figure 4b shows the result of comparison between the predictive values and actual stenotic ratios when the ANN constructed by the 109 patients was applied to the different set of patients with esophageal cancer (21 patients). The correlation coefficient was 0.812 ($p < 0.001$).

DISCUSSION

Definitive chemoradiation is currently used for the treatment of local esophageal cancer, as well as in conjunction with radical surgery and endoscopic resection. In Japan, squamous cell carcinoma is the most common histologically confirmed esophageal cancer and is considered to have high radiosensitivity. Some reports have indicated various advantages of definitive chemoradiation for managing localized esophageal cancer (1–4, 14–18). Some oncologists advocate that a nonsurgical approach with definitive chemoradiotherapy be regarded as the standard treatment for this disease (19–22). Recently, some reports have suggested that chemoradiation may be considered equivalent to surgery in terms of survival (3–5). In light of these suggestions, it may be desirable to choose an appropriate treatment option on an individual patient basis. An evaluation of the risk of developing esophageal stenosis in association with radiotherapy might be considered a useful guide when choosing a treatment option, as well as an important piece of information to provide when obtaining a patient's informed consent before radiotherapy. If severe esophageal stenosis develops despite tumor regression by radiotherapy, patients will experience dysphagia, which will decrease their quality of life. For esophageal stenosis after radiotherapy, there are several palliative treatments, including balloon dilatation, endoscopic placement of esophageal stents, and bypass operation. However, their clinical outcomes are not satisfactory: there is a high probability of restenosis for balloon dilation and a high incidence of severe complications for placement of esophageal stents and bypass operation after radiotherapy.

There have been few reports on the risk factors for esophageal stenosis after radiotherapy for esophageal cancer. In our preliminary study on 47 patients with locally advanced esophageal cancer, extent of involved circumference and wall thickness of the tumor region

Table 5. Correlation between number of risk factors and proportion of stenosis levels

No. of risk factors	No. of patients	Frequency of each stenosis level (%)			
		1	2	3	4
0	44	93	7	0	0
1	20	70	25	5	0
2	26	42	23	16	19
3	19	5	16	21	58

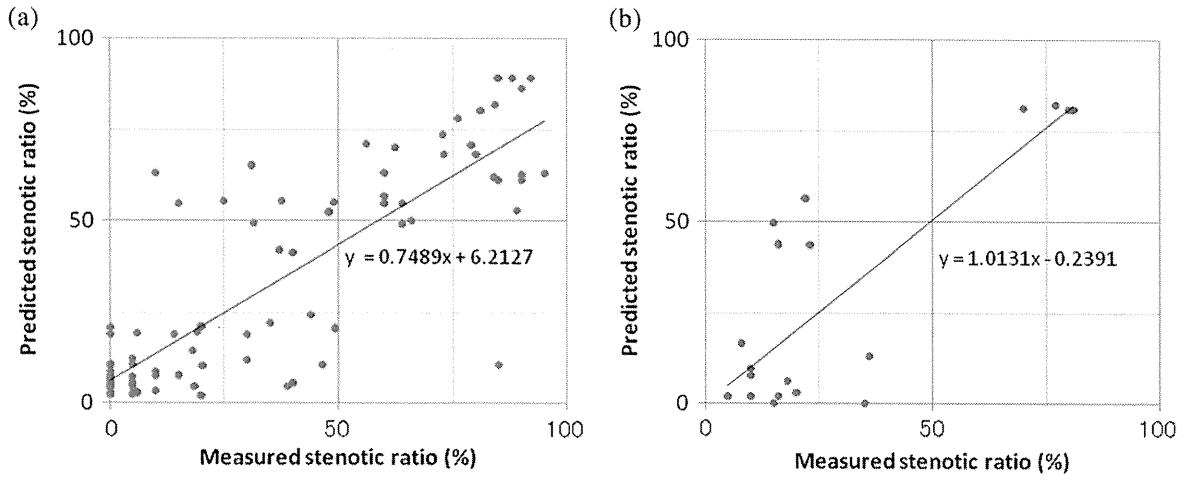

Fig. 4. (a) Relationship between the stenotic ratios predicted by the artificial neural network and the actual stenotic ratios determined by radiation oncologists in 109 patients. The correlation coefficient was 0.864 ($p < 0.001$). (b) Validation analysis comparing the stenotic ratios predicted by the ANN with the actual stenotic ratios for a different set of 21 patients. The correlation coefficient was 0.812 ($p < 0.001$).

were suggested to be useful risk factors to predict esophageal stenosis associated with tumor regression in radiotherapy (7). In the present study of 109 patients, which also included cases of early esophageal cancer, it was confirmed that extent of involved circumference and wall thickness of the tumor region were significantly correlated with severity of esophageal stenosis after radiotherapy. In addition, T stage also showed significant correlation to the frequency and severity of esophageal stenosis in this study. On the basis of these findings, we consider that T stage (i.e., depth of invasion) should be added to the risk factors predicting esophageal stenosis associated with tumor regression in radiotherapy for all staged patients with esophageal cancers. To verify whether these three factors (i.e., T stage, extent of involved circumference, and wall thickness of the tumor region) are able to predict severity of esophageal stenosis after radiotherapy, we used an ANN to predict esophageal stenosis in our patients. The results showed that the esophageal stenotic ratio predicted by the ANN using these three factors was significantly correlated with the actual esophageal stenotic ratio. In addition, we applied the ANN constructed by the 109 cases to a different set of 21 cases, and the resultant correlation value was 0.812. Therefore, these factors were considered to be significant, valid predictive factors for esophageal stenosis after radiotherapy. The ANN using these factors may provide radiation oncologists with a stenotic ratio having predictive value before treatment on a case-by-case basis.

Esophageal stenosis during radiotherapy may be caused by fibrosis or ischemic change during the process of tumor reduction, but the detailed mechanisms of these effects have not been clarified yet. Seaman *et al.* (23) reported that patients with dysphagia after radiotherapy to the chest and neck show histologic evidence of fibrosis of the submucosa, and hyalinization of the smooth muscle layers of the esophagus. These processes probably include the accumulation of macrophages and increased local levels of proinflammatory cytokines induced by radiation (24, 25), producing edema and fibrosis in the mucosal and submucosal layer that may secondarily affect the underlying muscles (26). These processes may be much more pronounced in and around the shrinking tumors that respond well to radiotherapy. As a result, the involved circumference may show the most significant correlation with the severity of esophageal stenosis after radiotherapy. Similar results have been documented in endoscopic resection for early esophageal cancer. Katada *et al.* (27) reported that a circumferential mucosal defect involving more than three fourths of the circumference of the esophagus after endoscopic mucosal resection was significantly associated with the subsequent development of esophageal stenosis. Mizuta *et al.* (28) reported that the most frequent complication after endoscopic submucosal dissection was esophageal stenosis, for which the sizes of the tumor and mucosal defect were significant predictive factors; they concluded that, in cases with a lesion with a diameter greater than half the circumference of the esophagus, great care must be taken because of the high risk of post–endoscopic submucosal dissection stenosis.

In the INT-0123, the 2-year survival rates for 50.4 Gy and 64.8 Gy radiation with short-term infusion chemotherapy for locally esophageal cancer were 40% and 31%, respectively, in which statistically significant differences appeared (29). In the United States and other Western countries, therefore, radiation of 50.4 Gy combined with chemotherapy using CDDP and 5-FU with full-dose short-term infusion is a standard regimen for locally esophageal cancer. In many patients of our study, the median radiation dose of 65 Gy was delivered in combination with low-dose protracted infusion of CDDP and 5-FU. Radiation of 60–70 Gy with low-dose protracted infusion chemotherapy has been reported to achieve a relatively promising outcome and low incidence of high-grade toxicity, including esophageal stenosis, so radiotherapy of 60–70 Gy with a low-dose protracted infusion chemotherapy has remained as a popular regimen for locally

advanced esophageal cancer in Japan (1, 30–35) It needs to be investigated in future studies whether differences of radiation dose or chemotherapy regimen affect the frequency or severity of esophageal stenosis associated with tumor regression.

This study was performed retrospectively to determine the predictive factors correlated with the degree of esophageal stenosis according to objective evaluation using esophagography within 3 months after the completion of radiotherapy. It is also considered important clinically to evaluate whether the proposed predictive factors are correlated with clinical symptoms, aggressiveness of the procedure performed to overcome the esophageal stenosis, or esophageal stenosis as late side effects. However, in this retrospective study, objective evaluations of them were considered difficult to be performed for the following reasons. The information about the clinical symptoms was obtained from patient charts. There was no questionnaire used to assess the symptoms objectively. In general, the choice of treatment procedure for esophageal stenosis was determined on the basis of various factors, including the patient's condition, patient's request, and physician's preferences. Intended to evaluate disease control, in the majority of patients follow-up examinations were performed with esophagoscopy and CT from 3 months after the completion of radiotherapy. In future prospective studies, the proposed prediction system in this study needs to be validated for its reliability to predict esophageal stenosis, clinical symptoms, and the need for intervention for esophageal stenosis.

In conclusion, our study showed that T stage, extent of involved circumference, and esophageal wall thickness of the tumor region were useful predictive factors for acute esophageal stenosis associated with tumor regression in radiotherapy for esophageal cancer. The ANN using these three predictive factors can be used for determination of an optimal treatment strategy for esophageal cancer.

REFERENCES

1. Hironaka S, Ohtsu A, Boku N, *et al.* Nonrandomized comparison between definitive chemoradiotherapy and radical surgery in patients with T2–3 Nany M0 squamous cell carcinoma of the esophagus. *Int J Radiat Oncol Biol Phys* 2003;57:425–443.
2. Fréchette E, Buck DA, Kaplan BJ, *et al.* Esophageal cancer: Outcomes of surgery, neoadjuvant chemotherapy, and three-dimension conformal radiotherapy. *J Surg Oncol* 2004;87:68–74.
3. Stahl M, Stuschke M, Lehmann N, *et al.* Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. *J Clin Oncol* 2005;23: 2310–2317.
4. Gebski V, Burmeister B, Smithers BM, *et al.* Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: A meta-analysis. *Lancet Oncol* 2007;8: 226–234.
5. Bedenne L, Michel P, Bouché O, *et al.* Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. *J Clin Oncol* 2007; 25:1160–1168.
6. Sun XD, Yu JM, Fan XL, *et al.* Randomized clinical study of surgery versus radiotherapy alone in the treatment of resectable esophageal cancer in the chest. *Zhonghua Zhong Liu Za Zhi* 2006;28:784–787.
7. Atsumi K, Shioyama Y, Nakamura K, *et al.* Predictive factors of esophageal stenosis associated with tumor regression in radiation therapy for locally advanced esophageal cancer. *J Radiat Res* 2010;51:9–14.
8. International Union Against Cancer. TNM classification of malignant tumors. 6th fully revised ed. New York: Springer-Verlag; 2002.
9. Japanese Society for Esophageal Disease. Guidelines for clinical and pathologic studies on carcinoma of the esophagus. 8th ed. Tokyo: Kanehara; 1992.
10. Abe H, Ashizawa K, Li F, *et al.* Artificial neural networks (ANNs) for differential diagnosis of interstitial lung disease: Results of a simulation test with actual clinical cases. *Acad Radiol* 2004;11:29–37.
11. Fukushima A, Ashizawa K, Yamaguchi T, *et al.* Application of an artificial neural network to high-resolution CT: Usefulness in differential diagnosis of diffuse lung disease. *AJR Am J Roentgenol* 2004;183:297–305.
12. Matake K, Yoshimitsu K, Kumazawa S, *et al.* Usefulness of artificial neural network for differential diagnosis of hepatic masses on CT images. *Acad Radiol* 2006;13:951–962.
13. Yamashita K, Yoshiura T, Arimura H, *et al.* Performance evaluation of radiologists with artificial neural network for differential diagnosis of intra-axial cerebral tumors on MR images. *Am J Neuroradiol* 2008;29:1153–1158.
14. Enzinger PC, Mayer RJ. Esophageal cancer. *N Engl J Med* 2003;349:2241–2252.
15. Coia LR. Chemoradiation as primary management of esophageal cancer. *Semin Oncol* 1994;21:483–492.
16. Liao Z, Cox JD, Komaki R. Radiochemotherapy of esophageal cancer. *J Thorac Oncol* 2007;2:553–568.
17. Nemoto K. Current management of patients with esophageal cancer. *Nippon Acta Radiologica* 2002;66:132–137.
18. Wong RK, Malthaner RA, Zuraw L, *et al.* Combined modality radiotherapy and chemotherapy in nonsurgical management of localized carcinoma of the esophagus: A practice guideline. *Int J Radiat Oncol Biol Phys* 2003;55:930–942.
19. Herskovic A, Martz K, al-Sarraf M, *et al.* Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med* 1992; 326:1593–1598.
20. Cooper JS, Guo MD, Herskovic A, *et al.* Chemoradiotherapy of locally advanced esophageal cancer: Long-term follow-up of a prospective randomized trial (RTOG 85-01). *JAMA* 1999; 281:1623–1627.
21. Araújo CM, Souhami L, Gil RA, *et al.* A randomized trial comparing radiation therapy versus concomitant radiation therapy and chemotherapy in carcinoma of the thoracic esophagus. *Cancer* 1991;67:2258–2261.
22. Wilson KS, Lim JT. Primary chemo-radiotherapy and selective oesophagectomy for oesophageal cancer: Goal of cure with organ preservation. *Radiother Oncol* 2000;54: 129–134.
23. Seaman WB, Ackerman LV. The effect of radiation on the esophagus. *Radiology* 1957;68:534–541.
24. Handschel J, Sunderkötter C, Prott FJ, *et al.* Increase in RM3/1-positive macrophages in radiation-induced oral mucositis. *J Pathol* 2001;193:242–247.
25. Sonis ST, Peterson RL, Edwards LJ, *et al.* Defining mechanisms of action of interleukin-11 on the progression of radiation-induced oral mucositis in hamsters. *Oral Oncol* 2000;36:373–381.
26. Eisbruch A, Schwartz M, Rasch C, *et al.* Dysphagia and aspiration after chemoradiotherapy for head-and-neck cancer:

Which anatomic structures are affected and can they be spared by IMRT? *Int J Radiat Oncol Biol Phys* 2004;60: 1425–1439.
27. Katada C, Muto M, Manabe T, *et al.* Esophageal stenosis after endoscopic mucosal resection of superficial esophageal lesions. *Gastrointest Endosc* 2003;57:165–169.
28. Mizuta H, Nishimori I, Kuratani Y, *et al.* Predictive factors for esophageal stenosis after endoscopic submucosal dissection for superficial esophageal cancer. *Dis Esophagus* 2009;22:626–631.
29. Minsky BD, Pajak TF, Ginsberg RJ, *et al.* INT 0123 (Radiation Therapy Oncology Group 94–05) phase III trial of combined-modality therapy for esophageal cancer: High-dose versus standard-dose radiation therapy. *J Clin Oncol* 2002;20:1167–1174.
30. Sai H, Mitsumori M, Yamauchi C, *et al.* Concurrent chemoradiotherapy for esophageal cancer: Comparison between intermittent standard-dose cisplatin with 5-fluorouracil and daily low-dose cisplatin with continuous infusion of 5-fluorouracil. *Int J Clin Oncol* 2004;9:149–153.
31. Sasamoto R, Sakai K, Inakoshi H, *et al.* Long-term results of chemoradiotherapy for locally advanced esophageal cancer, using daily low-dose 5-fluorouracil and cis-diammine-dichloro-platinum (CDDP). *Int J Clin Oncol* 2007;12:25–30.
32. Kenjo M, Uno T, Murakami Y, *et al.* Radiation therapy for esophageal cancer in Japan: Results of the Patterns of Care Study 1999-2001. *Int J Radiat Oncol Biol Phys* 2009;10(75): 357–363.
33. Sakayauchi T, Nemoto K, Ishioka C, *et al.* Comparison of cisplatin and 5-fluorouracil chemotherapy protocols combined with concurrent radiotherapy for esophageal cancer. *Jpn J Radiol* 2009;4(27):131–137.
34. Nishimura Y, Mitsumori M, Hiraoka M, *et al.* A randomized phase II study of cisplatin/5-FU concurrent chemoradiotherapy for esophageal cancer: Short-term infusion versus protracted infusion chemotherapy (KROSG0101/JROSG021). *Radiother Oncol* 2009;92:260–265.
35. Ishikura S, Nihei K, Ohtsu A, *et al.* Long-term toxicity after definitive chemoradiotherapy for squamous cell carcinoma of the thoracic esophagus. *J Clin Oncol* 2003;21:2697–2702.

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;

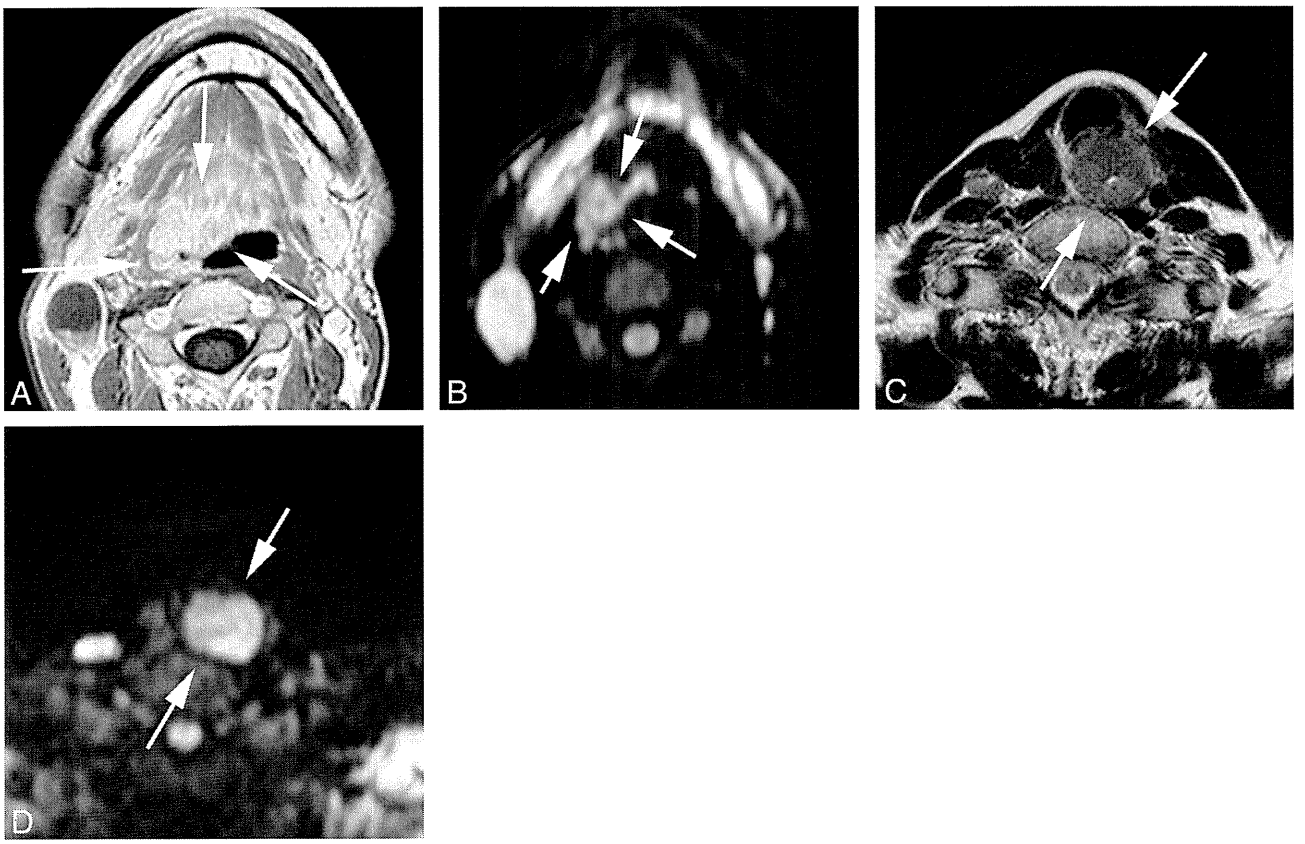

Fig 1. Representative images of local control and failure cases obtained before treatment. *A* and *B*, Transverse gadolinium-enhanced T1-weighted and DWI (b = 1000 s/mm^2) of a local-control case (oropharyngeal cancer, 30s, male, T4N2M0, high ADC before treatment = 0.63 × 10^{-3} mm^2/s). *C* and *D*,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

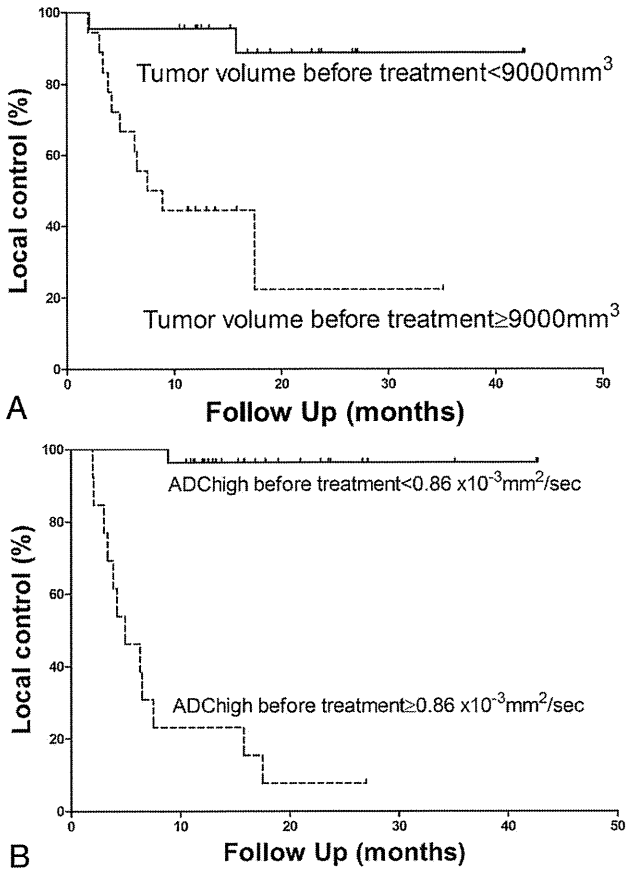

Fig 2. Comparison of local-control curves in the validation study. *A*, Comparison of the local-control curves between tumor volume before treatment <9000 mm^3 (solid line) and ≥9000 mm^3 (dashed line) ($P = .0002$). *B*, Comparison of the local-control curves between high ADC before treatment <0.86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

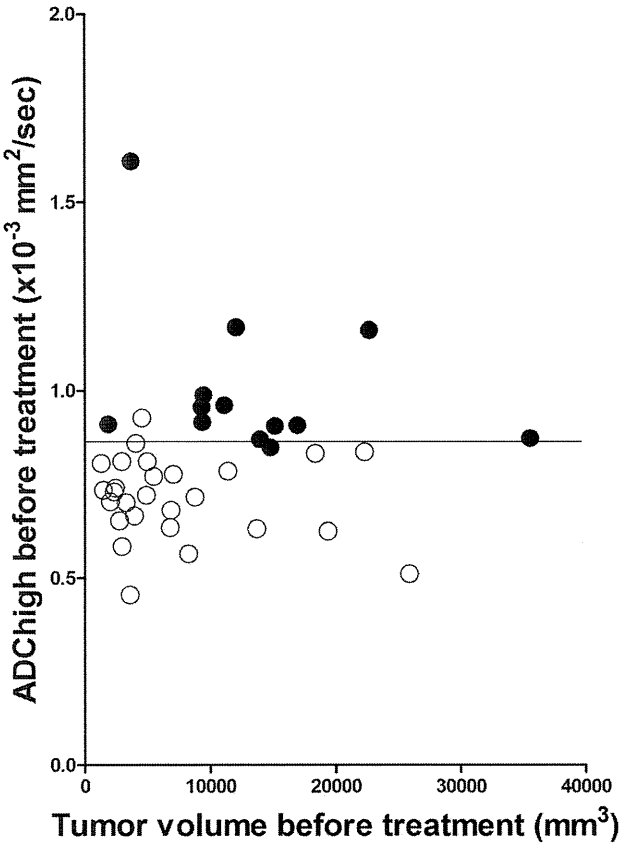

Fig 3. Scatterplot of tumor volume before treatment versus high ADC before treatment. Open and closed circles indicate local control and failure cases, respectively. Horizontal line indicates a threshold value of 0.86 × 10^{-3} mm^2/s for high ADC before treatment.

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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References

1. Tanner JE. **Self diffusion of water in frog muscle.** *Biophys J* 1979;28:107–16
2. Tanner JE. **Intracellular diffusion of water.** *Arch Biochem Biophys* 1983;224:416–28
3. Hatakenaka M, Matsuo Y, Setoguchi T, et al. **Alteration of proton diffusivity associated with passive muscle extension and contraction.** *J Magn Reson Imaging* 2008;27:932–37
4. Hatakenaka M, Yabuuchi H, Sunami S, et al. **Joint position affects muscle proton diffusion: evaluation with a 3-T MR system.** *AJR Am J Roentgenol* 2010;194:W208–11
5. Wang J, Takashima S, Takayama F, et al. **Head and neck lesions: characterization with diffusion-weighted echo-planar MR imaging.** *Radiology* 2001;220:621–30
6. Guo Y, Cai YQ, Cai ZL, et al. **Differentiation of clinically benign and malignant breast lesions using diffusion-weighted imaging.** *J Magn Reson Imaging* 2002;16:172–78
7. Eida S, Sumi M, Sakihama N, et al. **Apparent diffusion coefficient mapping of salivary gland tumors: prediction of the benignancy and malignancy.** *AJNR Am J Neuroradiol* 2007;28:116–21
8. Sumi M, Ichikawa Y, Nakamura T. **Diagnostic ability of apparent diffusion coefficients for lymphomas and carcinomas in the pharynx.** *Eur Radiol* 2007;17:2631–37
9. Hatakenaka M, Soeda H, Yabuuchi H, et al. **Apparent diffusion coefficients of breast tumors: clinical application.** *Magn Reson Med Sci* 2008;7:23–29
10. Mardor Y, Roth Y, Ochershvilli A, et al. **Pretreatment prediction of brain tumors' response to radiation therapy using high b-value diffusion-weighted MRI.** *Neoplasia* 2004;6:136–42
11. Oh J, Henry RG, Pirzkall A, et al. **Survival analysis in patients with glioblastoma multiforme: predictive value of choline-to-N-acetylaspartate index, apparent diffusion coefficient, and relative cerebral blood volume.** *J Magn Reson Imaging* 2004;19:546–54
12. Higano S, Yun X, Kumabe T, et al. **Malignant astrocytic tumors: clinical importance of apparent diffusion coefficient in prediction of grade and prognosis.** *Radiology* 2006;241:839–46
13. Murakami R, Sugahara T, Nakamura H, et al. **Malignant supratentorial astrocytoma treated with postoperative radiation therapy: prognostic value of pretreatment quantitative diffusion-weighted MR imaging.** *Radiology* 2007;243:493–99
14. Chenevert TL, Stegman LD, Taylor JM, et al. **Diffusion magnetic resonance imaging: an early surrogate marker of therapeutic efficacy in brain tumors.** *J Natl Cancer Inst* 2000;92:2029–36
15. Mardor Y, Pfeffer R, Spiegelmann R, et al. **Early detection of response to radiation therapy in patients with brain malignancies using conventional and high b-value diffusion-weighted magnetic resonance imaging.** *J Clin Oncol* 2003;21:1094–100
16. Hamstra DA, Chenevert TL, Moffat BA, et al. **Evaluation of the functional diffusion map as an early biomarker of time-to-progression and overall survival in high-grade glioma.** *Proc Natl Acad Sci U S A* 2005;102:16759–64
17. Moffat BA, Chenevert TL, Lawrence TS, et al. **Functional diffusion map: a noninvasive MRI biomarker for early stratification of clinical brain tumor response.** *Proc Natl Acad Sci U S A* 2005;102:5524–29
18. Koh DM, Scurr E, Collins D, et al. **Predicting response of colorectal hepatic metastasis: value of pretreatment apparent diffusion coefficients.** *AJR Am J Roentgenol* 2007;188:1001–08
19. Kato H, Kanematsu M, Tanaka O, et al. **Head and neck squamous cell carcinoma: usefulness of diffusion-weighted MR imaging in the prediction of a neoadjuvant therapeutic effect.** *Eur Radiol* 2009;19:103–09
20. Kim S, Loevner L, Quon H, et al. **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* 2009;15:986–94
21. Vandecaveye V, Dirix P, De Keyzer F, et al. **Predictive value of diffusion-weighted magnetic resonance imaging during chemoradiotherapy for head and neck squamous cell carcinoma.** *Eur Radiol* 2010;20:1703–14
22. King AD, Mo FK, Yu KH, et al. **Squamous cell carcinoma of the head and neck: diffusion-weighted MR imaging for prediction and monitoring of treatment response.** *Eur Radiol* 2010;20:2213–20
23. Hatakenaka M, Nakamura K, Yabuuchi H, et al. **Pretreatment apparent diffu-**