Clinical utility of apparent diffusion coefficient and diffusion-weighted magnetic resonance imaging for resectability assessment of head and neck tumors with skull base invasion

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Abstract
Background: The usefulness of apparent diffusion coefficient (ADC) and diffusion-weighted magnetic resonance imaging (DWI) in the detection of malignant tumors has been reported. The purpose of this study is to clarify the role of ADC and DWI for diagnosis of skull base tumors.

Methods: A total of 27 patients with head and neck tumors with skull base invasions undergoing skull base surgery were enrolled in this study. Pathological findings of dural invasion and bone invasion were compared with the diagnostic imaging.

Results: Advanced magnetic resonance imaging techniques revealed that ADC values in regions of pathological bone and dural invasions were significantly lower than in regions of no invasion. The area under the curve of ADC in bone invasions and dural invasions were 0.957 and 0.894, respectively.

Conclusions: Our findings indicate that ADC and DWI are useful tools for the diagnosis of head and neck tumors with skull base invasion.

KEYWORDS
ADC, DWI, head and neck cancer, MRI, skull base tumor

1 | BACKGROUND

Skull base tumors (SBTs) are rare tumors that consist of sinonasal malignancies, malignancies of the temporal bone and orbit, and so forth. Multimodality treatment, which includes surgery and radiotherapy, is used for SBTs. The surgical procedures used for these tumors vary. Recently, endoscopic skull base surgery has been shown to be useful as a minimally invasive treatment for such tumors; however, there are limitations to this approach.1

The accurate diagnosis of the invasion of a tumor, such as frontal sinus invasion, sphenoid sinus invasion, anterior skull base invasion, or dural and cavernous sinus invasion, is important to create an effective treatment plan when considering the operability and the surgical approach (endoscopic or craniofacial resection). There is
a real danger of false positives when using diagnostic imaging for SBTs. For example, dural enhancement by gadolinium enhanced magnetic resonance imaging (eMRI) does not mean that there has been a dural invasion but may indicate inflammation or reactive chance. Abnormal findings, including bone destruction and osteosclerosis, indicated by computed tomography (CT) also do not always indicate bone invasion. Ideally, radiologic observations should be correlated with surgical and/or pathologic findings. Imaging studies of the skull base, however, present considerable difficulties in getting such verification because of the relatively inaccessible anatomical location. Thus, few studies have examined the relationship between pathological spread and diagnostic images in SBTs. Mortuaire et al suggested that CT/magnetic resonance imaging (MRI) mapping cannot replace the accurate assessment of pathological tumor extension during surgery in sinonasal malignancies. Although Bier et al described the low occurrence of false positives of dural enhancement by eMRI in carcinomatous meningeosis, no conclusion has been reached about the accuracy of the pathological progression and CT/MRI findings in SBTs.

Diffusion-weighted MRI (DWI) is an MRI technique that measures signals from extracellular diffusion of water molecules. It is widely used for detection of acute ischemic stroke and the differentiation of acute stroke from other processes that manifest with sudden neurologic deficits. DWI also provides adjunctive information for neoplasms. Apparent diffusion coefficient (ADC) is a quantification of DWI. The large number of meta-analysis was reported associated with usefulness of ADC value to distinguish breast malignancies from benign tumors. DWI and ADC have also been shown to be effective for the diagnosis of many neoplastic regions, including head and neck tumors. This study aimed to elucidate the role of ADC and DWI for the diagnosis of head and neck tumors with skull base invasion.

2 MATERIALS AND METHODS

2.1 Subjects

A total of 27 patients with SBTs who underwent skull base surgery at the Tohoku University Hospital from November 2012 to November 2018 were enrolled in this study. Secondary or recurrent tumors after surgery were excluded. Diagnostic imaging, including CT, eMRI, DWI, and ADC map, was performed before surgery. The histological findings of resected bone and dural as well as all tumors were compared with diagnostic imaging obtained prior to surgery. Institutional review boards approved this study and written informed consent was obtained from all individual participants included in the study. The procedures followed were in accordance with the Helsinki declaration.

2.2 CT technique

CT scans of the head and neck were obtained using 64 or 128 detector-row CT scanner (SOMATOM Definition; SOMATOM Definition FLASH, Siemens Medical Solutions, Erlangen, Germany) with the following parameters: 120 kV, and 72 mAs, gantry rotation speed of 0.5 second per rotation, collimation 128 × 0.6 mm², and pitch factor 1.0. Nonionic iodine contrast agents (Omnipaque, iohexol, Daiichi-Sankyo, Tokyo, Japan; Iopamiron, Iopamidol, Bayer HealthCare, Berlin, Germany) were injected intravenously as 475 mgI/Kg. Transverse images were reconstructed at 1 mm thickness, and coronal images were at 5 mm thickness, on a 512 × 512 matrix. We reconstructed all images with the soft-tissue window settings and bone algorithms.

2.3 MRI technique

MRI examinations were performed using a 1.5T MR imager (Achieva 1.5T Nova Dual, Philips Medical Systems, Eindhoven, The Netherlands) or a 3.0T MR imager (Achieva 3.0T dStream or Ingenia 3.0T CX, Philips Medical Systems, Eindhoven, The Netherlands) with head and neck coil. MRI protocols included the following: transverse T1-weighted images (450-734/10-12 [repetition time (ms)/echo time (ms)], field of view 210-230 mm, reconstruction matrix 512 × 512, 560 × 560, 640 × 640, or 672 × 672, section thickness 5-6 mm), transverse and coronal fat-suppressed T2-weighted images (3500-6281/58-100, field of view 210-230 mm, matrix 512 × 512, 560 × 560, or 640 × 640, section thickness 5-6 mm), transverse and coronal fat-suppressed post-contrast T1-weighted images (450-626/10-12, field of view 210-230 mm, reconstruction matrix 512 × 512, 560 × 560, or 672 × 672, section thickness 5-6 mm) with intravenous infusion of 0.2 mL/kg body weight gadolinium contrast agents (Magnescope, meglumine gadoterate, Guerbet Japan, Tokyo, Japan; Gadovist, Gadobutrol, Bayer HealthCare, Berlin, Germany), transverse diffusion-weighted echo-planar or turbo spin echo images (3500-6877/62-80, field of view 200-250 mm, reconstruction matrix 256 × 256 or 288 × 288, section thickness 5-6 mm, and b factor of 0 and 1000 seconds/mm²). ADC maps were reconstructed by DWI of the different b factor, b = 0 and 1000 s/m² on workstation. The regions of interest (ROIs) were located with the consensus of three
observers (I. K., T. O., and S. W.) manually to avoid the vessels and cystic parts of the tumors, in reference to contrast-enhanced transverse T1-weighted images. ADC values of two ROIs in both the main tumor and the regions of skull base invasion were analyzed.

### 2.4 CT and MR factor analysis

CT and MRI results were interpreted independently by three of the authors (T. M., M. S., and I. K.) before the histological diagnoses. Abnormal CT findings included bone destruction (complete destruction was defined as transmural skull base destruction and incomplete destruction was defined as partial and/or heterogeneous skull base destruction) and osteosclerosis. Dural enhancement was determined by eMRI. DWI and ADC values of abnormal findings by CT or eMRI were also analyzed. These MRI and CT factors were then compared with the histological findings.

### 2.5 Statistical analysis

Mann Whitney $U$ test was applied to compare ADC values between histological dural invasion or bone invasion positive and negative. Receiver-operator-characteristic (ROC) curves of each histologic type were also analyzed. Cut-off values were demonstrated by the Youden index. For the analyses, Excel 2016 and Stat flex ver.6 (Artech Co., Ltd., Japan) was used. The statistically significant level was 0.05.

### 3 RESULTS

Two representative cases (cases 1 and 2) with squamous cell carcinomas (SCCs) ex Inverted Papilloma (IP) are shown in Figure 1. Initially, CT revealed abnormal findings in both cases, including incomplete bone destruction in case 1 and complete bone destruction in case 2. Subsequent eMRI revealed dural enhancement in both cases.

**FIGURE 1** A, Case 1 (IP-SCC without histological bone invasion): Incomplete destruction by CT (arrow), dural enhancement by eMRI (arrowheads), low signal intensity by DWI (arrow) and high ADC value (arrow) are shown. Histologically, no malignant findings were observed in the resected bone. B, Case 2 (IP-SCC with histological bone invasion): Complete destruction by CT (arrow), dural enhancement by eMRI (arrowheads), high signal intensity by DWI (arrow) and low ADC value (arrow) are shown. Histologically, cancer infiltration was observed in the resected bone. ADC, apparent diffusion coefficient; CT, computed tomography; DWI, diffusion-weighted MR imaging; eMRI, enhanced magnetic resonance imaging; IP, inverted papilloma; SCC, squamous cell carcinomas [Color figure can be viewed at wileyonlinelibrary.com]
However, DWI and ADC values were distinctly different between them. Case 1 had a low signal intensity by DWI ($b = 1000$) compared with normal sinonasal mucosa and a high ADC value ($2.11 \times 10^{-3} \text{ mm}^2/\text{s}$). In contrast, case 2 exhibited a high signal intensity by DWI ($b = 1000$) and a low ADC value ($1.30 \times 10^{-3} \text{ mm}^2/\text{s}$). The histological findings of infiltrated bone specimens revealed no malignancy in case 1 and a SCC in case 2 (Figure 1). However, there was no histological dural invasion in either of those cases.

The characteristics of the 27 patients in this study are shown in Table 1. The cases included 20 males and 7 females, aged from 26 to 73 years (median age: 56 years). Twenty-two patients had sinonasal malignancies, two had malignancies of the orbit, and three had soft tissue malignancies. The histological diagnoses included olfactory neuroblastoma (ONB) in seven cases, SCC in seven cases, malignant peripheral nerve sheath tumor in two cases, primitive neuroectodermal tumor in two cases, adenocarcinoma in two cases, and others in seven cases. The histological findings of the 27 patients revealed skull base bone invasions in 18 cases (66.7%) and dural invasions in 10 cases (37.0%).

CT was performed in all 27 cases (Table 2) and bone destruction was found in 23 cases. No osteosclerosis was found in this cohort. Complete and incomplete bone destruction were found in 17 and 6 cases, respectively. Compared with the histological findings, 14 of the 17 cases (82.4%) in the complete destruction group demonstrated histological bone invasion. In contrast, one of the six cases (16.7%) in the incomplete destruction group demonstrated histological bone invasion. Three of the four cases in the no abnormal findings by CT group demonstrated histological bone invasion.

eMRI was performed in all 27 cases (Table 3). Among them, positive dural enhancement was found in 18 cases. Compared with the histological findings, 9 of the 18 cases (50.0%) in the dural enhancement group demonstrated histological dural invasion. In contrast, one of the nine cases (11.1%) in the negative for dural enhancement group demonstrated histological dural invasion.

DWI and ADC values of the main tumor and the region of skull base invasion were obtained in all 27 cases. The ADC value of each main tumor exhibited no significant differences by sex, age, tumor site, and histology and histological bone invasion (Table 4). However, ADC values of the main tumor with histological dural invasion were significantly lower than those with no dural invasion ($P = .013$).

ADC values of regions of skull base invasion were analyzed (Figure 2). ADC values with histological bone invasion ($0.65-1.88$, median $0.95 \times 10^{-3} \text{ mm}^2/\text{s}$) were lower than those with no bone invasion ($1.30-2.40$, median $1.94 \times 10^{-3} \text{ mm}^2/\text{s}$), which is a statistically significant difference ($P = .0001$) (Figure 2A). Also, the ADC values of the regions of skull base invasion with histological dural invasion ($0.65-1.12$, median $0.875 \times 10^{-3} \text{ mm}^2/\text{s}$) were lower than those with no dural invasion ($0.86-2.40$, median $1.34 \times 10^{-3} \text{ mm}^2/\text{s}$), which is a statistically significant difference ($P = .001$) (Figure 2B).

ROC curves of histological bone or dural invasions by ADC values of the regions of skull base invasion are also shown in Figure 2. The area under the curve (AUC) of bone and dural invasions were 0.957 and 0.894, respectively. Cut-off values by ADC values were calculated as 1.34 for bone invasions (Sensitivity: 88.9%, Specificity 88.9%, positive predictive value (PPV) 94.1%, negative

| **Table 1** Characteristics of patients in this study |
|-----------------|------------|-----------|
| **Factor**      | **Category** | **No. of patients** |
| **Sex**         | Male       | 20        |
|                 | Female     | 7         |
| **Age**         | <56        | 13        |
|                 | ≥56        | 14        |
| **Site**        | Nasal cavity/ethmoid sinus | 17 |
|                 | Maxillary sinus | 4 |
|                 | Frontal sinus | 1 |
|                 | Orbit      | 2         |
|                 | Soft tissue | 3         |
| **Histology**   | ONB        | 7         |
|                 | SCC        | 7         |
|                 | MPNST      | 2         |
|                 | PNET       | 2         |
|                 | AC         | 2         |
|                 | EHE        | 1         |
|                 | SFT        | 1         |
|                 | Small cell ca. | 1 |
|                 | OS         | 1         |
|                 | US         | 1         |
|                 | Sebaceus ca. | 1 |
|                 | ACC        | 1         |
| **Bone invasion** | Yes        | 18        |
|                 | No         | 9         |
| **Dural invasion** | Yes       | 10        |
|                 | No         | 17        |

Abbreviations: AC, adenocarcinoma; ACC, adenoid cystic carcinoma; EHE, epithelioid hemangioendothelioma; MPNST, malignant peripheral nerve sheath tumor; ONB, olfactory neuroblastoma; OS, osteosarcoma; PNET, primitive neuroectodermal tumor; SCC, squamous cell carcinoma; SFT, solitary fibrous tumor; US, undifferentiated sarcoma.
predictive value (NPV) 80.0%) and 1.12 for dural invasions (Sensitivity: 90.0%, Specificity: 82.4%, PPV: 75.0%, and NPV: 93.3%) by the Youden index.

To improve the accuracy of bone or dural invasion detection, the ratio of ADC values in regions of skull base invasion/main tumor was also calculated (Figure 3). The ADC ratio of (skull base invasion/main tumor) with histological bone invasion (0.75-1.62, median 1.09) was lower than those with no bone invasion (1.26-3.56, median 1.54), which is a statistically significant difference ($P = .017$) (Figure 3A). However, there was no significant difference in dural invasion (Figure 3B). The ROC curve of histological bone or dural invasion by the ADC ratio of (skull base invasion/main tumor) is also shown in Figure 3. The AUC of bone and dural invasions was 0.944 and 0.688, respectively. Each cut-off value and CT or eMRI finding were merged (Table 5). For the detection of bone invasion, CT + ADC values did not improve any of the parameters of accuracy when compared with ADC values alone. However, eMRI + ADC values for dural invasions improved the specificity and PPV over ADC alone.

Two representative cases (cases 3 and 4) with SBTs with cystic regions are shown in Figure 4. eMRI demonstrated a cystic part and a capsule in both cases; however, a low ADC value was found only in case 3 (Figure 4A). Subsequent histological examination revealed bone and dural invasions were present in both cases, so the ADC value indicated a false negative in case 4 (Figure 4B).

**DISCUSSION**

CT and eMRI are considered the gold standard for the pretreatment diagnosis of SBTs; however, bone destruction by CT and dural enhancement by eMRI can result in false positives. In this study, the sensitivity and specificity for bone invasion by CT was 83.3% and 11.1%,
respectively. However, the sensitivity and specificity of eMRI to detect dural invasion in this study were 90% and 47%, respectively. The low specificity indicated that incomplete bone destruction and dural enhancement may not be good metrics for determining an appropriate course of action for skull base surgery. Additionally, intracranial infiltration through cranial foramen could not be pointed out in three of four cases by CT. In patients with perineural spread and subsequent cavernous sinus involvement, MRI may detect the abnormal findings well before foraminal erosion is evident by CT.2,14

Using ADC, six of the eight cases with false positives for bone destruction by CT were diagnosed properly. Additionally, six of the nine cases that resulted in false positives for dural enhancement by eMRI were diagnosed properly by ADC. In three false-negative cases by CT where microscopic bone invasion of the cranial foramen or orbital roof was indicated, the ADC value of the surrounding tissue of all three cases was lower than $1.34 \times 10^{-3} \text{ mm}^2/\text{s}$ cut-off value indicating that bone invasion was present. One false negative case by eMRI was an ONB with brain infiltration. That case had limited brain invasion and no surrounding dural enhancement. However, it was clearly detected by ADC (ADC value $0.74 \times 10^{-3} \text{ mm}^2/\text{s}$). These results highlight the potential of ADC for a pretreatment diagnosis of SBTs.

ADC values with histological bone and dural invasion were significantly lower than those with no bone invasion. Furthermore, ROC curves demonstrated the high

![FIGURE 2](image-url)
FIGURE 3  The ADC ratio of (skull base invasion/main tumor) of bone and dural invasions. A, Box and whisker plot of ADC ratio in histological bone invasions. B, Box and whisker plot of ADC ratio in histological dural invasions. Maximum number, 25% percentile, median, 75% percentile and minimum numbers are shown in box and whisker plots. *P < .05. C, ROC curve of ADC ratios in histological bone invasions. D, ROC curve of ADC ratios in histological dural invasions. ADC, apparent diffusion coefficient; ROC, receiver-operator-characteristic

<table>
<thead>
<tr>
<th>Bone invasion</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
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<tr>
<td>CT</td>
<td>83.3%</td>
<td>11.1%</td>
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<td>ADC (cut-off 1.34)</td>
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<td>88.9%</td>
<td>94.1%</td>
<td>80.0%</td>
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<td>CT + ADC (cut-off 1.34)</td>
<td>72.2%</td>
<td>88.9%</td>
<td>92.9%</td>
<td>61.5%</td>
</tr>
<tr>
<td>Dural invasion</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>eMRI</td>
<td>90%</td>
<td>47%</td>
<td>50%</td>
<td>89%</td>
</tr>
<tr>
<td>ADC (cut-off 1.13)</td>
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<td>82%</td>
<td>75%</td>
<td>93%</td>
</tr>
<tr>
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<td>88%</td>
<td>80%</td>
<td>88%</td>
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</table>

Abbreviations: ADC, apparent diffusion coefficient; CT, computed tomography; eMRI, enhanced magnetic resonance imaging; MRI, magnetic resonance imaging.
AUC of both bone and dural invasions. Regarding the pretreatment diagnosis, the biggest issue is whether the skull base invasion site is a benign lesion (such as inflammation or papilloma) or cancer, ADC could distinguish the IP and SCC as in previous reports. Because benign tumors and malignant tumors have different safety margin setting methods, this study could help determine if performing endoscopic surgery or craniofacial surgery is a better approach.

There were two cases with histological bone invasion in which ADC did not show a malignant pattern by the cut-off value. One was an ONB patient whose intracranial infiltration site involved a large cystic change. ROIs cannot be set when there are few solid components. The other instance was an epithelioid hemangioendothelioma with microinvasion. There was only one instance where the ADC did not show a pattern of malignancy but a histologically dural invasion was present. That case was the patient with ONB described earlier.

The limitations of this study include the small number of patients and the diversity of the tumor locations and histology as well as the MRI equipment used and technical parameters, such as magnetic field (1.5 and 3 T), DW sequences (EPI and TSE DWI), and TR/TE have great influence on the ADC values. ADC values have been reported to vary by histological type in head and neck malignancies although there was no difference between histology and subsite in this study. Thus, the ratio of ADC values in regions of skull base invasion/main tumor was also calculated in this study. Though AUC of the ROC curve was low, it may be true to compare the main tumor and the base of the skull base. Further examinations using a larger cohort and/or a prospective study are needed.

5 CONCLUSION

Our results indicate that ADC can be a useful quantitative preoperative tool in the treatment of SBTs. These results also suggest that ADC and DWI values may be useful to assess the resectability of SBTs.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ETHICS STATEMENT

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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