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Comparison of Imaging Findings between Human Papillomavirus-positive and -Negative Squamous Cell Carcinomas of the Maxillary Sinus

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ABSTRACT

Objectives: This study aimed to assess the efficacy of imaging findings when differentiating between human papillomavirus (HPV)-positive and -negative squamous cell carcinomas (SCCs) of the maxillary sinus.

Material and Methods: This study included 37 patients with histopathologically and immunohistochemically confirmed SCCs of the maxillary sinus (three HPV positive and 34 HPV negative). Apparent diffusion coefficients (ADCs), MR signal intensities, CT findings, and maximum standardized uptake (SUVmax) were correlated with the two pathologies.

Results: The minimum ADC (ADCmin) was significantly lower in HPV-positive SCCs than in HPV-negative SCCs (0.50 ± 0.02 vs. $0.70 \pm 0.13 \times 10^{-3}$ mm^2/s, $P < 0.01$). The mean ADC (ADCmean) was not significantly different between HPV-positive SCCs and HPV-negative SCCs (0.84 ± 0.07 vs. $0.97 \pm 0.18 \times 10^{-3}$ mm^2/s, $P = 0.18$). The areas under the receiver operating characteristic curves for ADCmin and ADCmean were 0.986 ($P < 0.01$) and 0.754 ($P < 0.05$), respectively. The sensitivity and specificity, with a threshold of ADCmin (0.516×10^{-3} mm^2/s) for a diagnosis of HPV-positive SCCs, were 100% and 96%, respectively. However, no significant differences were observed in MR signal intensities, CT findings, and SUVmax between HPV-positive and HPV-negative SCCs.

Conclusion: ADCmin is a useful parameter for the differentiation of HPV-positive and HPV-negative SCCs of the maxillary sinus.

Keywords: Squamous cell carcinoma, Maxillary sinus, Human papillomavirus, Magnetic resonance imaging, Diffusion-weighted imaging

INTRODUCTION

Infection with human papillomavirus (HPV), particularly HPV16 and HPV18, is a well-established cause for the development of head-and-neck squamous cell carcinomas (HNSCCs). Recently, the incidence of HPV-positive HNSCCs has been increasing in some European countries and the United States.[1-5] HPV-positive and HPV-negative HNSCCs are considered to be different disease entities. HPV-positive HNSCCs are more likely to occur in men who are non-smokers, non-drinkers, younger in age and have a higher socioeconomic status. HPV-positive HNSCCs most often originate from the oropharynx and frequently present with regional lymph node metastasis. Histologically, these tumors are usually high grade and they commonly exhibit basaloid morphology. The patients with HPV-positive HNSCCs have higher

response rates to treatment and have better clinical outcomes compared to patients with HPV-negative HNSCCs.[1-5] Similarly, HPV-positive sinonasal SCCs show significantly improved survival rates in comparison to HPV-negative sinonasal SCCs because of better responses to radiotherapy and chemotherapy.[6-8]

The differences in CT and MR imaging findings between HPV-positive and HPV-negative oropharyngeal SCCs have already been reported previously.[9-14] On CT images, HPV-positive oropharyngeal SCCs frequently have well-demarcated primary lesions and cystic nodal metastases compared to HPV-negative oropharyngeal SCCs.[9,10] In addition, diffusion-weighted (DW) MR imaging with apparent diffusion coefficient (ADC) measurements can be useful for differentiating HPV-positive and HPV-negative HNSCCs because of a relatively stronger diffusion restriction of HPV-positive HNSCCs.[11-14] However, to the best of our knowledge, there has been no study that has reported differences in imaging findings between HPV-positive and HPV-negative SCCs of the maxillary sinus. Therefore, we aimed to evaluate the efficacy of imaging findings to differentiate between HPV-positive and HPV-negative SCCs of the maxillary sinus.

MATERIAL AND METHODS

Patients

The present study was approved by the Human Research Committee of the Institutional Review Board of our hospital and complied with the guidelines of the Health Insurance Portability and Accountability Act of 1996. The requirement for informed consent was waived due to the retrospective nature of this study. From the hospital's electronic medical record system, we reviewed data of patients who were histopathologically diagnosed with SCCs of the maxillary sinus using tissue biopsies or surgical resections between January 2005 and December 2017. We obtained 54 consecutive patients with SCCs of the maxillary sinus. Among them, 47 patients with SCCs of the maxillary sinus underwent pre-operative CT and MR imaging, but 10 of 47 patients were excluded from this study because we could not obtain paraffin-embedded tissue samples for immunostaining.

In total, 37 patients with SCCs of the maxillary sinus were included in this study (30 males and 7 females; age range, 38–82 years; median age, 63 years). Because p16 positivity is considered a surrogate marker of oncogenic HPV infection due to its high sensitivity, simplicity, and low cost,[15] HPV status was determined by p16-INK4a immunohistochemistry staining. p16 expression was defined as positive if strong and diffuse nuclear and cytoplasmic staining was observed in ≥70% of the tumor specimens.[16] The result of p16-INK4a immunohistochemistry staining indicated p16 expression was positive in 3 (8%) patients and negative in the remaining 34 (92%) patients. Histological subtypes of p16-positive SCCs were non-keratinizing in the three patients, whereas those of p16-negative SCCs were keratinizing in 12 patients and non-keratinizing in 22 patients.

CT imaging

All 37 patients were examined using multidetector-row CT. CT imaging was performed using a 8-slice CT scanner (LightSpeed Ultra; GE Healthcare, Milwaukee, WI, USA), 16-slice CT scanner (LightSpeed 16; GE Healthcare, Milwaukee, WI, USA), or a 64-slice CT scanner (Brilliance CT 64; Philips Medical Systems, Best, The Netherlands). Unenhanced CT images were obtained in all 37 patients, and contrast-enhanced CT images were obtained in 32 patients. Contrast-enhanced CT images were obtained 45 s after initiating intravenous bolus injection of 100 mL of non-ionic iodine contrast material (Omnipaque 300 [300 mg of iodine per ml], Daiichi Sankyo, Tokyo, Japan or Optiray 240 [240 mg of iodine per ml], Mallinckrodt Inc., Hazelwood, MO, USA) at an injection rate of 2 mL/s. Axial and coronal multiplanar reconstruction images were reconstructed with 2.5 mm section thickness and no overlap. These CT images were reconstructed using bone and soft-tissue algorithms.

MR imaging

MR imaging was performed using a 1.5-T MR imaging system (Intera Achieva 1.5 T Pulsar; Philips Medical Systems, Best, The Netherlands). All MR images were obtained at a section thickness of 4 mm with 1 mm intersection gap with a field of view of 20 × 20 cm. Axial T2-weighted fast spin-echo images (TR/TE, 3646–5710/90–100 msec) and axial T1-weighted spin-echo images (TR/TE, 620–827/9–15 msec) were obtained for all 37 patients. In 33 patients, axial fat-suppressed gadolinium-enhanced T1-weighted spin-echo images (TR/TE, 630–840/9–15 msec) were obtained after the intravenous injection of 0.1 mmol/kg of gadopentetate dimeglumine (Magnevist, Bayer HealthCare, Leverkusen, Germany) or gadobutrol (Gadavist, Bayer HealthCare, Leverkusen, Germany). In 26 patients (three patients with HPV-positive SCCs and 23 patients with HPV-negative SCCs), short-tau inversion recovery single-shot spin-echo echo-planar DW images (TR/TE/TI, 4,419–5,504/72/170 msec; *b*-value, 0 and 1000 s/mm^2) were obtained.

^{18}F-fluorodeoxyglucose (FDG) PET/CT

Whole-body PET/CT (Biograph Sensation 16; Siemens Medical Solutions, Malvern, PA, USA) from the skull to mid-thigh was performed for 20 patients (two patients with HPV-positive SCCs and 18 patients with HPV-

negative SCCs). Briefly, after at least 4 h of fasting, patients received an intravenous injection of ^{18}F-FDG (185 MBq). Blood glucose levels were checked in all patients before FDG injection, and no patient had a blood glucose level >150 mg/dL. Approximately 60 min after FDG injection, CT and subsequent whole-body PET were performed. Technical parameters of the 16 row multidetector CT were a gantry rotation speed of 0.5 s, a table speed of 24 mm per a gantry rotation, and quiet-breathing data acquisition. Transverse images were reconstructed with 2 mm section thickness and no overlap. Oral or intravenous contrast agent was not used for CT. PET had an axial view of 16.2 cm per bed position with an intersectional gap of 3.75 mm in one bed position, which necessitated data acquisition in six or seven bed positions. Axial PET images were obtained using an imaging matrix of 256 × 256 and a field of view of 50 × 50 cm.

Imaging assessment

The CT and MR images were individually reviewed by two radiologists with 20 and 6 years of post-training experience of head-and-neck imaging. In addition, they were unaware of the results of p16-INK4a immunohistochemistry staining. Any discrepancies between the two reviewers were resolved by achieving a consensus through discussion.

For qualitative assessment, predominant tumor growth patterns, remaining sinus wall within the tumor, intratumoral necrosis, cervical lymphadenopathy, and tumor extension (nasal cavity, orbit, subcutaneous tissue, retroantral fat pad, perineural spread, and intracranial) were evaluated on CT or MR images.[17] Predominant tumor growth patterns were classified as one of three patterns, that is, destructive, permeative, and expansile types. A destructive type was defined as an invasive lesion accompanied by extensive bone destruction and no bony expansion of the adjacent maxillary sinus walls. A permeative-type tumor was defined as an invasive lesion that crossed the sinus wall with the original form of the sinus walls remaining as a linear structure within the tumor. An expansile-type tumor was defined as a non-invasive lesion accompanied by bony expansion or erosion of the adjacent maxillary sinus walls. Remaining sinus walls within the tumor were defined by the presence of sinus wall within the tumor. Tumor necrosis was defined as focal unenhanced areas on contrast-enhanced images or marked hyperintense areas on T2-weighted images. Cervical lymphadenopathy was considered to be metastatic nodes when the minimum diameter exceeded 1.0 cm.

For quantitative measurement, the radiologist measured the maximum diameter of the tumor and defined the regions of interest (ROIs) in unenhanced MR sequences. ROIs were determined as broadly as possible in the tumors as widely as possible while excluding areas of necrosis according to the T2-weghted images or contrast-enhanced T1-weighted images. The reviewer also measured the signal intensities of the spinal cord or brain stem at the same level as the tumors and then the tumor-to-spinal cord/brain stem signal intensity ratios were calculated. ADC values ($\times 10^{-3}$ mm^2/s) were measured on ADC maps by placing ROIs over the tumors. ADC values were obtained as ADCmin (lowest tumor voxel value within the ROI) and ADCmean (mean ADC within the ROI). As semi-quantitative analysis of FDG uptake, the reviewer determined the maximum standardized uptake value (SUVmax) of each lesion.

Statistical analysis

Statistical analyses were performed with SPSS version 22.0 (SPSS, Inc., an IBM Company, Chicago, Illinois, USA) and MedCalc 12.7.2 (MedCalc Software, Ostend, Belgium). A Chi-squared test or Fisher's exact test was used to compare the qualitative results (tumor growth patterns, remaining sinus wall within the tumor, intratumoral necrosis, cervical lymphadenopathy, and tumor extension to the nasal cavity, orbit, subcutaneous tissue, retroantral fat pad, perineural spread, and intracranial) between HPV-positive and HPV-negative SCCs. A Mann–Whitney U-test was used to compare the quantitative results (maximum diameter of tumor, MR signal intensities, ADC values, and SUVmax) between HPV-positive and HPV-negative SCCs. Receiver operating characteristic curve analysis was used to determine the performance of ADCmin and ADCmean. $P < 0.05$ was considered to be statistically significant.

RESULTS

The qualitative imaging results for HPV-positive and HPV-negative SCCs of the maxillary sinus are summarized in Table 1. No significant differences were found for tumor growth patterns, remaining sinus wall within the tumor (33% vs. 47%; $P = 0.56$), intratumoral necrosis (100% vs. 85%; $P = 0.64$), cervical lymphadenopathy (0% vs. 12%; $P = 0.70$), and tumor extension to the nasal cavity (100% vs. 76%; $P = 0.47$), orbit (67% vs. 47%; $P = 0.48$), subcutaneous tissue (33% vs. 59%; $P = 0.40$), retroantral fat pad (100% vs. 76%; $P = 0.47$), perineural spread (0% vs. 18%; $P = 0.58$), and intracranial (0% vs. 15%; $P = 0.64$) between HPV-positive and HPV-negative SCCs of the maxillary sinus, respectively.

The quantitative measurements of HPV-positive and HPV-negative SCCs of the maxillary sinus are summarized in Table 2. The ADCmin was significantly lower in HPV-positive SCCs than in HPV-negative SCCs (0.50 ± 0.02 vs. $0.70 \pm 0.13 \times 10^{-3}$ mm^2/s, $P < 0.01$), whereas the ADCmean was not significantly different between HPV-positive SCCs and HPV-negative SCCs (0.84 ± 0.07 vs. $0.97 \pm 0.18 \times 10^{-3}$ mm^2/s, $P = 0.18$) [Figures 1 and 2]. The areas under the receiver operating characteristic curves for ADCmin and ADCmean were 0.986 ($P < 0.01$) and 0.754 ($P < 0.05$),

Table 1: Qualitative imaging findings of HPV-positive and HPV-negative SCCs of the maxillary sinus.

	HPV positive (*n*=3)	HPV negative (*n*=34)	*P*-value
Predominant growth pattern			
Destructive	2 (67)	28 (82)	
Permeative	1 (33)	3 (9)	
Expansile	0 (0)	3 (9)	
Remaining sinus wall within the tumor	1 (33)	16 (47)	0.562
Intratumoral necrosis	3 (100)	29 (85)	0.638
Cervical lymphadenopathy	0 (0)	4 (12)	0.702
Tumor extension			
Nasal cavity	3 (100)	26 (76)	0.47
Orbit	2 (67)	16 (47)	0.479
Subcutaneous tissue	1 (33)	20 (59)	0.396
Retroantral fat pad	3 (100)	26 (76)	0.47
Perineural spread	0 (0)	6 (18)	0.579
Intracranial	0 (0	5 (15)	0.638

SCC: Squamous cell carcinoma. Data are numbers of patients, and numbers in parentheses are frequencies expressed as percentages

Table 2: Quantitative measurements of HPV-positive and HPV-negative SCCs of the maxillary sinus.

	HPV positive (*n*=3)	HPV negative (*n*=34)	*P*-value
Maximum diameter (mm)	54.0±12.2	50.8±14.5	0.693
Conventional MR images			
SIR on T1-weighted images	0.87±0.03	0.95±0.15	0.118
SIR on T2-weighted images	1.20±0.26	1.20±0.26	0.896
DW images	(*n*=3)	(*n*=23)	
SIR on DW images	1.35±0.16	1.16±0.38	0.275
ADCmin ($\times 10^{-3}$ mm^2/s)	0.50±0.02	0.70±0.13	0.002*
ADCmean ($\times 10^{-3}$ mm^2/s)	0.84±0.07	0.97±0.18	0.182
FDG-PET/CT	(*n*=2)	(*n*=18)	
SUVmax	14.0±0.44	18.0±5.37	0.379

SCC: Squamous cell carcinoma, SIR: Signal intensities ratio, DW: Diffusion weighted, ADC: Apparent diffusion coefficient, FDG: Fluorodeoxyglucose, SUVmax: Maximum standardized uptake value. Data are shown as the mean±1 standard deviation. *ADCmin of HPV positive was significantly lower than that of HPV negative (P<0.01)

respectively [Figure 3]. The sensitivity and specificity using a threshold of ADCmin (0.516×10^{-3} mm^2/s) for the diagnosis of HPV-positive SCCs were 100% and 96%, respectively. The sensitivity and specificity using a threshold of ADCmean (0.897×10^{-3} mm^2/s) for a diagnosis of HPV-positive SCCs were 100% and 61%, respectively.

No significant differences were observed in terms of the maximum diameter of the tumor (54.0 ± 12.2 vs. 50.8 ± 14.5 mm, P = 0.69), MR signal intensity ratios on T1-weigted images (0.87 ± 0.03 vs. 0.95 ± 0.15, P = 0.12), T2-weigthed images (1.20 ± 0.26 vs. 1.20 ± 0.26, P = 0.90), DW images (1.35 ± 0.16 vs. 1.16 ± 0.38, P = 0.28), and SUVmax (14.0 ± 0.44 vs. 18.0 ± 5.37, P = 0.38) between HPV-positive and HPV-negative SCCs of the maxillary sinus, respectively.

DISCUSSION

Sinonasal SCCs account for <3% of all malignancies of the head and neck and are classified into two major histological subtypes: Keratinizing (60%) and non-keratinizing SCCs (40%). Other five histologic variants of HNSCCs include verrucous SCCs, papillary SCCs, spindle cell (sarcomatoid) SCCs, basaloid SCCs, and adenosquamous carcinomas. Environmental risk factors for sinonasal SCCs include occupational exposures such as wood dust and formaldehyde. Smoking may also play a role in the development of SCCs. HPV has also been implicated in the development of sinonasal SCCs through malignant transformation of inverted papillomas. A subgroup of sinonasal SCCs associated with HPV infection has a significantly better prognosis and is easily identified by p16-INK4a immunostaining. p16-INK4a immunostaining has 100% sensitivity and specificity for the detection of HPV-positive sinonasal SCCs.[6]

In this study, three of 37 (8%) patients with maxillary sinus SCCs were positive for p16 expression in this study, whereas the rates of HPV-positive sinonasal SCCs ranged from 20% to 32%.[6,8,14] It seems that a discrepancy between the results of our study and the previous studies exists. However, these previous studies included the study population with both paranasal SCCs and nasal SCCs. Actually, 16 of 26 (62%) patients with nasal SCCs were positive for HPV.[7] Because inverted papillomas usually occur in the nasal cavity, nasal SCCs have a higher incidence of HPV positivity compared to paranasal SCCs.

In the present study, ADCmin was significantly lower in HPV-positive maxillary sinus SCCs than in HPV-negative tumors and an appropriate threshold of ADCmin could accurately differentiate between HPV-positive and HPV-negative maxillary sinus SCCs. de Perrot *et al.* reported that ADCmean and median ADCs were significantly lower in HPV-positive HNSCCs than in HPV-negative tumors.[12] Driessen *et al.* reported that positive HPV status in HNSCCs correlates with low ADC mean.[11] Nakahira *et al.* reported that ADCs could be used to predict HPV status in patients with oropharyngeal SCCs.[14] Zhou *et al.* also reported that ADCmean for high-risk HPV-positive uterine cervical SCCs was significantly lower than those for high-risk HPV-negative tumors.[18] These results would have been due to the histological characteristic that cell density is higher in HPV-positive SCCs than in HPV-negative tumors. Actually, HPV-positive SCCs are more likely to be non-keratinizing SCCs. Histopathologically, non-keratinizing SCCs show nests of

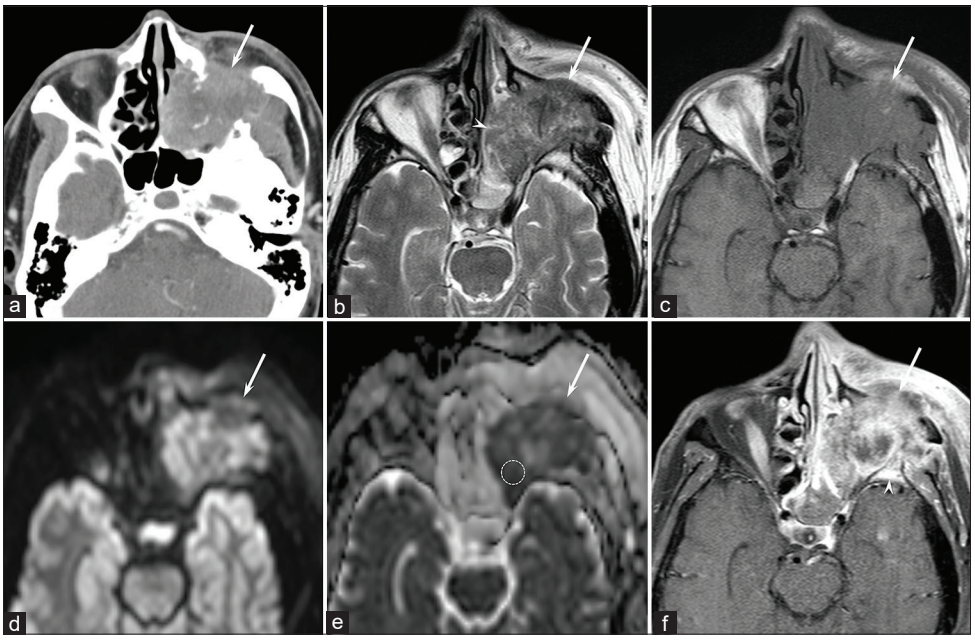

Figure 1: A 59-year-old man with HPV-positive SCC of the maxillary sinus. (a) Enhanced CT image shows a heterogeneously enhanced bulky mass (arrow) with destructive growth. (b) T2-weighted image (TR/TE, 4102/90 ms) shows a heterogeneously hypo- to hyperintense mass (arrow) with invasion of sphenoid sinus (arrowhead). (c) T1-weighted image (TR/TE, 630/9 ms) shows a hypointense mass (arrow). (d) Diffusion-weighted image (TR/TE/TI, 4954/72/170 ms) shows a heterogeneously hyperintense mass (arrow). (e) ADC map shows extremely low ADCmin (0.483×10^{-3} mm^2/s) and ADCmean (0.769×10^{-3} mm^2/s) (arrowhead). The dotted line shows the contours of region of interest placed on solid components. (f) Gadolinium-enhanced fat-suppressed T1-weighted image (TR/TE, 630/9 ms) shows a heterogeneously enhanced bulky mass with invasion of subcutaneous tissue (arrowhead) and sphenoid bone (arrowhead).

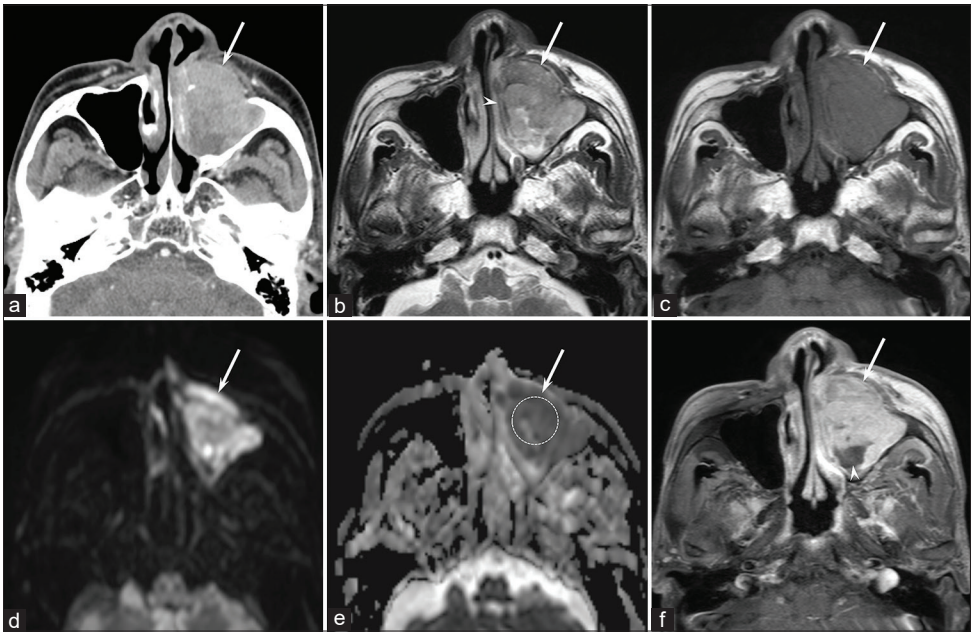

Figure 2: An 81-year-old man with HPV-negative SCC of the maxillary sinus. (a) Enhanced CT image shows a heterogeneously enhanced bulky mass (arrow) with destructive growth. (b) T2-weighted image (TR/TE, 3646/90 ms) shows a heterogeneously hypo- to hyperintense mass (arrow) with invasion of nasal cavity (arrowhead). (c) T1-weighted image (TR/TE, 662/15 ms) shows a hypointense mass (arrow). (d) Diffusion-weighted image (TR/TE/TI, 5490/72/170 ms) shows a heterogeneously hyperintense mass (arrow). (e) ADC map shows relatively low ADCmin (0.724×10^{-3} mm^2/s) and ADCmean (1.089×10^{-3} mm^2/s) (arrowhead). The dotted line shows the contours of region of interest placed on solid components. (f) Gadolinium-enhanced fat-suppressed T1-weighted image (TR/TE, 662/15 ms) shows a heterogeneously enhanced bulky mass with necrotic area (arrowhead) and invasion of subcutaneous tissue (arrow).

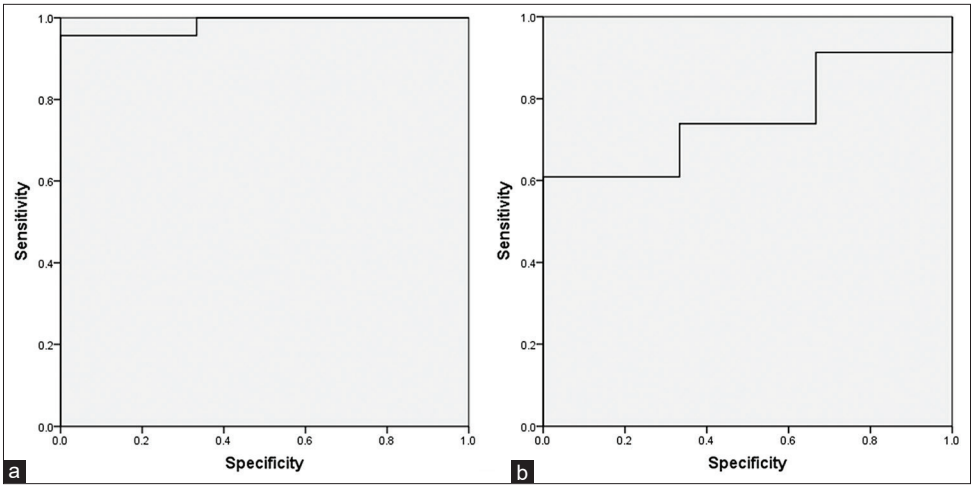

Figure 3: Receiver operating characteristic curves for ADC for a diagnosis of HPV-positive SCCs of the maxillary sinus. (a) Area under the curve for ADCmin is 0.986 ($P < 0.01$). (b) Area under the curve for ADCmean is 0.754 ($P < 0.05$).

tumor cells with little stromal reaction, minimal cytoplasm, and minimal areas of maturing squamous differentiation, whereas keratinizing SCCs show nests of tumor cells in desmoplastic stroma with foci of keratinization. These differences in histological findings would cause lower ADC values in HPV-positive SCCs than those in HPV-negative tumors. However, Schouten *et al*. reported that no significant association between ADC and HPV status was found in oropharyngeal SCCs.[13]

In this study, no significant differences in CT findings and MR signal intensity ratios were observed between HPV-positive and HPV-negative SCCs of the maxillary sinus. Cantrell *et al*. reported that HPV-positive oropharyngeal SCCs often had primary lesions with well-defined borders, whereas HPV-negative primaries had poorly defined borders more often and invaded into adjacent muscle.[10] However, because the majority of SCCs of the maxillary sinus show a destructive growth pattern,[17] no significant differences in growth patterns might be observed between HPV-positive and HPV-negative SCCs of the maxillary sinus.

In our study, no significant differences in SUVmax were found between HPV-positive and HPV-negative SCCs of the maxillary sinus. In the previous studies concerning oropharynx and oral cavity, nodal SUVmax was significantly higher in HPV-positive SCCs than in HPV-negative tumors, but no significant differences in SUVmax of the primary tumors were seen between HPV-positive and HPV-negative SCCs.[19,20] Unlike oropharyngeal and oral carcinomas, the incidence of lymph node metastasis from maxillary sinus carcinomas is relatively low (10–20%). Because cervical lymphadenopathy was not observed in three patients with HPV-positive maxillary sinus SCCs, we could not compare the nodal SUVmax between HPV-positive and HPV-negative SCCs of the maxillary sinus.

This study had several limitations. First, the cohort was relatively small because the study was conducted at a single institution. Because HPV-positive maxillary sinus SCCs are relatively rare, the number of HPV-positive maxillary sinus SCC cases was especially low. Second, because this was a retrospective study, we did not perform DW imaging and FDG-PET/CT for all patients. Third, we did not perform contrast-enhanced CT or MR imaging for all patients; and thus, the prevalence of intratumoral necrosis could not be assessed accurately.

CONCLUSION

ADCmin was significantly lower in HPV-positive SCCs of the maxillary sinus than in HPV-negative tumors, and an appropriate threshold of ADCmin could accurately differentiate between HPV-positive and HPV-negative SCCs of the maxillary sinus. Therefore, ADCmin is a useful parameter for the differentiation of HPV-positive and HPV-negative SCCs of the maxillary sinus. In contrast, no significant differences in MR signal intensities, CT findings, and SUVmax were observed between HPV-positive and HPV-negative SCCs of the maxillary sinus.

Declaration of patient consent

Institutional Review Board permission obtained for the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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