

# Value of apparent diffusion coefficient on MRI for prediction of histopathological type in anal fistula cancer

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## Abstract

The main histopathological types of anal fistula cancers are mucinous adenocarcinoma and tubular adenocarcinoma. The purpose of this study was to investigate the utility of the apparent diffusion coefficient (ADC) value in magnetic resonance imaging (MRI) to determine the histopathological type of an anal fistula cancer, and to investigate the relationship between ADC values and histopathological type (mucinous type or tubular carcinoma), clinical information, and surgical findings. We retrospectively identified 69 patients diagnosed with anal fistula cancer at our hospital from January 2013 to December 2021. Among them, we selected the patients diagnosed using the same 1.5-T MRI machine, underwent surgery, and a pathological sample was obtained during the operation. Finally, these 25 patients were selected for the analysis since they underwent the imaging scan using the same MRI machine. The ADC value was compared between mucinous and tubular adenocarcinomas, and between tumors at the Tis-T1-T2 and T3-T4 stages. Finally, 25 patients were selected. The mean age of the 25 patients included in the analysis was 60.8±13.3 years and all were males. The median ADC of anal fistula cancers was  $1.97 \times 10^{-3}$  mm<sup>2</sup>/s for mucinous adenocarcinomas and  $1.36 \times 10^{-3}$  mm<sup>2</sup>/s for tubular adenocarcinomas; this difference was statistically significant ( $P < .01$ ). Furthermore, the median ADC was  $1.62 \times 10^{-3}$  mm<sup>2</sup>/s for tumors in Tis-T1-T2 stages and  $2.01 \times 10^{-3}$  mm<sup>2</sup>/s for T3-T4 tumors ( $P = .02$ ). The ADC value in MR images may predict the histopathological type and depth of anal fistula cancers. Also, the different ADC values between Tis-T1-T2 and T3-T4 tumors could help predict the classification of progression.

**Abbreviations:** ADC = apparent diffusion coefficient, CD = Crohn disease, DWI = diffusion-weighted imaging, MRI = magnetic resonance imaging, ROC = receiver operating characteristic.

**Keywords:** anal fistula cancer, apparent diffusion coefficient, histopathological type

## 1. Introduction

Cancer arising from a fistula in the rectal-anal region (anal fistula cancer) is a malignant type of tumor associated with long-term anal fistulas and is reported to account for approximately 2% to 3% of colorectal cancers.<sup>1,2</sup> The World Health Organization states that anal fistula cancers originate from existing anal glands and fistula tracts.<sup>3</sup> The early diagnosis of anal fistula carcinoma is difficult because of the lack of early clinical symptoms due to its occurrence in a complex and intricate anal fistula tract.<sup>4</sup>

The histopathological types of anal fistula cancer are classified as mucinous adenocarcinoma, tubular adenocarcinoma, adenosquamous carcinoma, and squamous cell carcinoma. In a review of the clinical pathology and treatment results of 42

cases of anal fistula cancer at our hospital, the tumors identified were 32 mucinous adenocarcinomas, 8 tubular type adenocarcinomas, 1 adenosquamous carcinoma, and 1 squamous carcinoma.<sup>2</sup> In a review of the histopathology of 75 cases of anal fistula cancer in Crohn disease (CD), 51 were mucinous adenocarcinomas and 17 tubular type adenocarcinomas.<sup>15</sup>

Abdominoperineal resection is the first line of treatment for anal fistula cancers.<sup>6</sup> However, this surgery results in permanent colostomy, which significantly reduces the quality of life. In addition, extensive lymph node dissection may cause lymph node edema as a complication, and it is difficult to predict small lymph node metastases from preoperative imaging. Pre- and postoperative chemoradiotherapy are effective in rectal cancer, and the indications for anorectal-sparing surgery are expanding<sup>7,8</sup>; however, few reports focused on chemoradiotherapy specifically for

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

This study was approved by the Ethics Committee of our hospital (Application No. J-103, April 8, 2021).

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anal fistula cancer, and its therapeutic efficacy for these tumors remains unknown. Tubular adenocarcinomas are expected to respond to chemoradiotherapy, whereas the mucinous ones are resistant to these therapies.<sup>[6,9,10]</sup> Therefore, determining the histopathology of an anal fistula cancer before treatment is critical.

Magnetic resonance imaging (MRI) findings in anal fistula cancers reportedly show a mesh-like contrast pattern with a full, contrasted tumor on spin-echo MRI, fluid retention without a fibrotic capsule, and contrasted tumor margins.<sup>[11]</sup> T1- and T2-weighted images show heterogeneous high signal intensity.<sup>[11]</sup> Such imaging findings may reflect the characteristic features of mucinous carcinoma as a cystic tumor with a protein component within multifocal septal walls.<sup>[12]</sup> However, no previous report examined in detail the differences in MRI findings between mucinous and tubular adenocarcinomas.

The purpose of this study was to investigate the utility of the ADC value in MRI for the identification of the histopathological type of these tumors, and examine the relationship between ADC values and histopathological type (mucinous type or tubular carcinoma), clinical information, and surgical findings.

## 2. Methods

This study was based on a retrospective, cohort design; it was conducted in a single-center (Tokyo Yamate Medical Center) and approved by the Ethics Committee of our hospital (Application No. J-103, at April 8, 2021, approved change application form at March 25, 2023 Application No. J-171). Due to its retrospective nature, it was not possible to obtain prior informed consent from the patients; we used an opt-out form that was posted on the hospital website and at the reception desk of the Department of Radiology.

### 2.1. Case selection

Between January 2013 and December 2021, 69 cases of anal fistula cancer occurred in our hospital. These patients underwent surgery, and surgical pathological samples were obtained. Patients with concurrent colorectal cancer were excluded. Among them, we selected the patients diagnosed with anal fistula cancer using the same 1.5-T MRI machine, and these subjects were included in the analysis.

### 2.2. MRI protocol

The MRI scans were performed with a 1.5-T MRI system (MAGNETOM Aera, Siemens Healthcare, Erlangen, Germany), using an anal fistula protocol (Table 1). A noncontrast-enhanced MRI was used to obtain the images. All patients underwent

diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC) testing, T1-weighted (T1WI), and T2-weighted (T2WI) MRI.

### 2.3. Image evaluation

The MR images were evaluated by 2 radiologists with more than 20 years of experience (KT and SK); one is also specialized in anal fistula MRI diagnosis (SK). Both radiologists received information about the patient prior diagnosis of anal fistula cancer and the location of the lesion on MRI, and agreed on the area of the lesion.

The Digital Imaging and Communications in Medicine (DICOM) images were imported into the open-source image processing tool OsiriX (OsiriX Foundation, Geneva, Switzerland). The 2 radiologists used the MR images acquired with the anal fistula protocol as a reference to select the region of interest with diffusion restriction on DWI as the lesion area (DWI-region of interest) on the corresponding ADC image (Fig. 1).

### 2.4. Clinical findings

The clinical information was obtained from electronic medical records. Age at diagnosis, sex, and presence or absence of CD were included in the data for the analysis.

### 2.5. Surgical and pathological findings

The surgical findings were obtained from the records of the primary surgeon. The evaluation variables were the surgical technique and the presence or absence of lymph node metastases. The pathological findings were obtained from the diagnostic records of the pathologists. The evaluation variables were histopathological type, histological differentiation, depth, lymphatic invasion, venous invasion, and staging. Since the histopathological types of anal fistula cancer have a spectrum, the components of mucinous and tubular adenocarcinoma were compared. In accordance with the World Health Organization Colorectal Cancer Code, tumors with a prevalence of mucinous findings were classified as mucinous adenocarcinomas, and those with mainly tubular cells as tubular adenocarcinomas.

### 2.6. Statistical analysis

Statistical analysis was conducted with Easy-R (EZR), developed at the Omiya Medical Center of Jichi Medical University Hospital.<sup>[13]</sup>

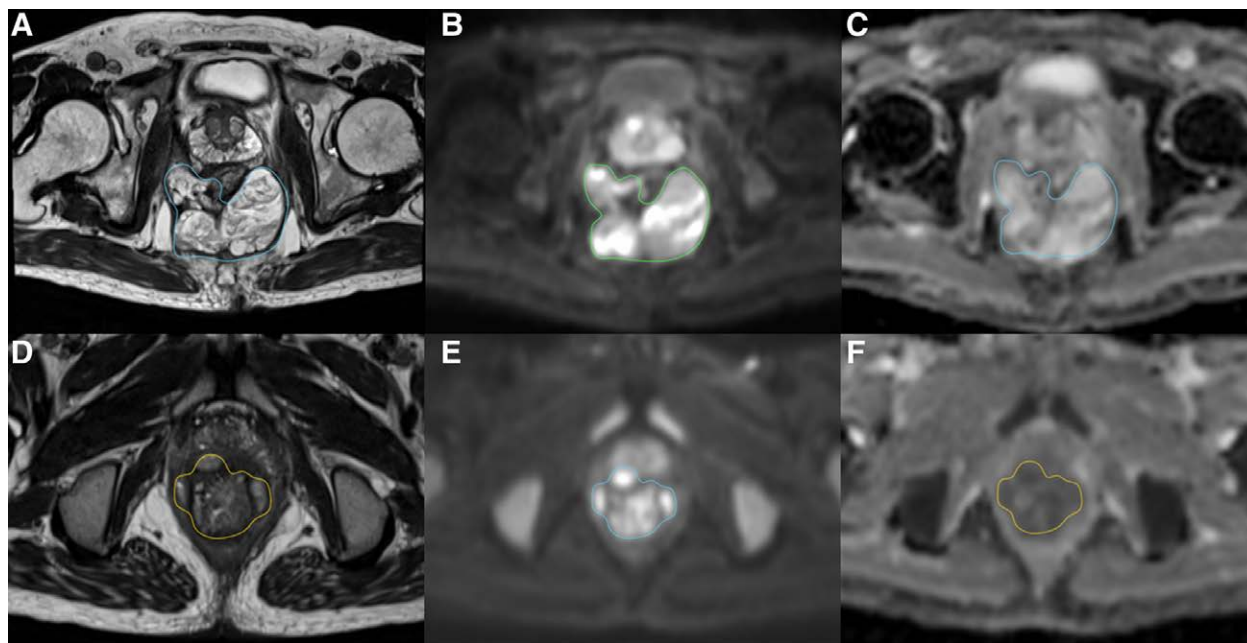
The Mann–Whitney *U* test was used to compare the radiological characteristics (median ADC) between different clinical, surgical, and pathological groups. A receiver operating

**Table 1**

**Sequence parameters for magnetic imaging of anal fistulae.**

Protocol	T2WI tse	DWI	T2WI space 3D	FS T2WI tse f-Dixon	T2WI tse	T1WI f3d Dixon pre (DCE)
Orientation	Sag	Tra	Tra	Obl-tra	Obl-cor	Obl-tra
TR (ms)	3400	5000	1100	3080	4179	7.13
TE (ms)	89	63	95	87	87	2.39/4.77
Slice thickness (mm)	3.5	6	–	3	3	3
FOV read (mm)	250	350	250	250	250	250
Slices	20	30	–	30	30	–
Distance factor (%)	20	10	–	20	20	–
Averages	1	–	1.5	1	2	1
Fat-suppressed	–	SPAIR	–	Fast Dixon	–	Dixon
<i>b</i> -value		0, 50, 800				
Scan time (s)	95	145	223	136	154	24

3D = 3-dimensional, Cor = coronal, DCE = dynamic contrast enhancement, DWI = diffusion-weighted imaging, f3d = flash 3-dimensional, FOV = field of view, FS T2WI = fat-suppressed T2-weighted magnetic resonance imaging, Obl = oblique, Sag = sagittal, SPAIR = spectral attenuated inversion recovery, T1WI = T1-weighted magnetic resonance imaging, T2WI = T2-weighted magnetic resonance imaging, TE = echo time, TR = repetition time, Tra = transverse, tse = turbo spin echo.



a: T2WI, b: DWI, c: ADC Muc Image  
d: T2WI, e: DWI, f: ADC Tub Image

**Figure 1.** MRI images. (a–c) T2WI, DWI, and ADC images of a mucinous adenocarcinoma; (d–f) T2WI, and DWI, and ADC images of a tubular adenocarcinoma. ADC = apparent diffusion coefficient, DWI = diffusion-weighted imaging, MRI = magnetic resonance imaging, T2WI = T2-weighted imaging.

characteristic (ROC) curve analysis was used to calculate the cutoff values and area under the curve showing the test efficacy. The Fisher test was used to examine the distributional bias. For all statistical tests,  $P < .05$  was set as the level of statistical significance.

### 3. Results

#### 3.1. Patients

Finally, 25 patients were selected. The mean age of the 25 patients included in the analysis was  $60.8 \pm 13.3$  years and all were males. All patients underwent rectal amputation; 24 of them also received pelvic lymphadenectomy. The histological types were 17 mucinous adenocarcinomas, 7 tubular adenocarcinoma, and 1 unclassifiable. Six patients had CD. Lymph node metastases were observed in 3 patients; as for the staging, Tis-T1-T2 and T3-T4 tumors were found in 10 and 15 patients, respectively. The median ADC was  $1.80$  (range:  $1.28$ – $2.27$ )  $\times 10^{-3}$   $\text{mm}^2/\text{s}$ .

#### 3.2. Comparison between surgical and pathological findings

**1.3.2. Histopathology.** The median ADC was  $1.97 \times 10^{-3}$   $\text{mm}^2/\text{s}$  in mucinous adenocarcinomas and  $1.36 \times 10^{-3}$   $\text{mm}^2/\text{s}$  in tubular adenocarcinomas, and there was a significant difference between these 2 groups ( $P = .005$ ). In the ROC analysis, the area under the curve was  $0.857$ , with a 95% confidence interval of  $0.627$  to  $1$ , when the ADC cutoff value was set at  $1.74$ . There were no statistically significant differences in age and lymph node metastases between patients with and without CD.

**2.3.2. Depth.** The median ADC was  $1.62 \times 10^{-3}$   $\text{mm}^2/\text{s}$  for the Tis-T1-T2 group and  $2.01 \times 10^{-3}$   $\text{mm}^2/\text{s}$  for the T3-T4 group, and the difference between the 2 groups was statistically significant ( $P = .02$ ). In the ROC analysis, the area under the curve was

$0.780$ , with a 95% confidence interval of  $0.595$  to  $0.965$ , when the cutoff value of ADC was set at  $1.96 \times 10^{-3}$   $\text{mm}^2/\text{s}$ . There were no significant differences in age, presence or absence of CD, or lymph node metastases between these 2 groups. Table 2 and Figure 2 summarize the above results.

### 4. Discussion

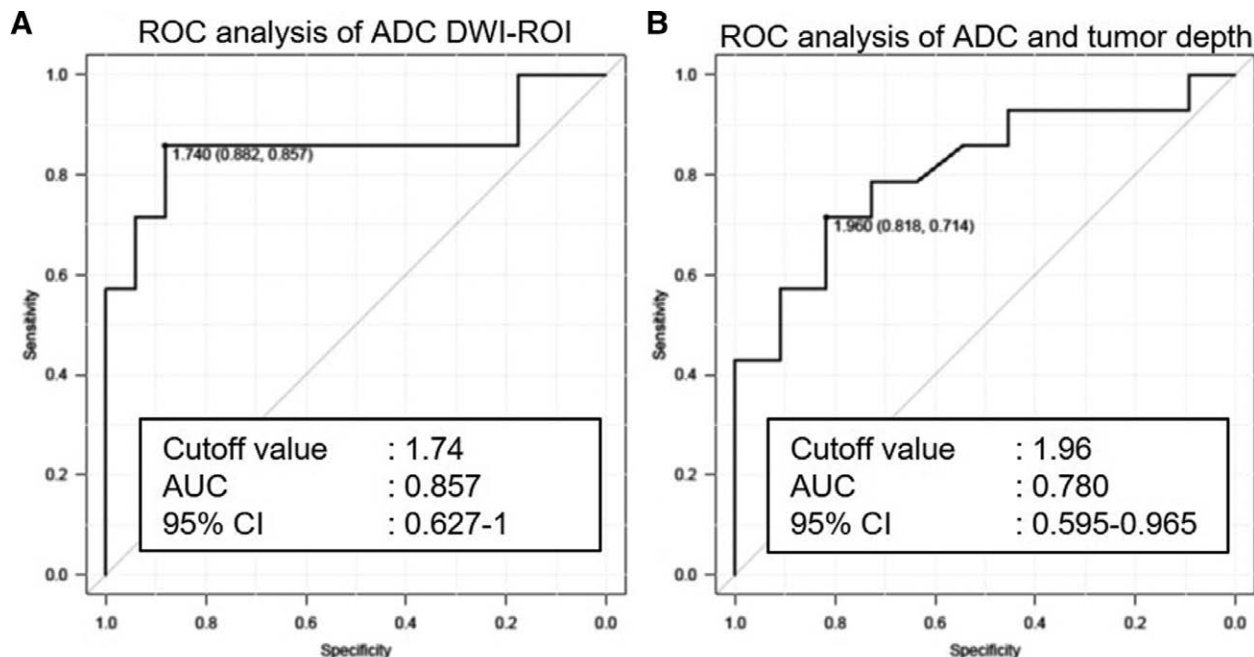
This study compared the imaging findings in anal fistula cancer in different surgical and pathological groups. The histopathological classification was 68% (17/25) mucinous and 28% (7/25) tubular adenocarcinomas. In a study of 42 cases of anal fistula cancers at our institution, we found 76% (32/42) mucinous and 19% (8/42) tubular adenocarcinomas.<sup>[2]</sup> In a study of 75 cases including anal fistula cancers related to CD, the histopathological types were reported as 68% (51/75) mucinous and 23% (17/75) tubular adenocarcinomas.<sup>[9]</sup> The findings of the present study were similar to the results of these reports, with frequencies of mucinous and tubular adenocarcinomas in anal fistula cancers of approximately 70% and 20%, respectively.

There are few studies on the treatment of anal fistula cancer, and reports are predominantly case reports. One case report described the operation and adjuvant FOLFOX6 chemotherapy in a patient with mucinous adenocarcinoma (anal fistula cancer).<sup>[14]</sup> In 5 cases of anal fistula cancer (4 mucinous adenocarcinomas and 1 nonmucinous adenocarcinoma), 1 patient (T3N1M0) received neoadjuvant chemoradiotherapy, 1 patient (T4N0M0) received chemotherapy, 1 patient underwent an operation for mucinous adenocarcinoma,<sup>[15]</sup> 2 patients (with mucinous adenocarcinoma) received radiation and chemotherapy, and 1 patient with lymph node metastasis died following distant metastasis.<sup>[16]</sup> From these reports, it is clear that the treatment strategy for anal fistula cancer is not established overseas. In Japan, there are few reports on anal fistula cancer. The standard treatment for anal fistula cancer is surgery. Operation and abdominoperineal resection was reportedly mainly performed in 15 patients with anal fistula cancer.<sup>[6]</sup> Furthermore, the protocol for chemotherapy is not established.

**Table 2**  
**Comparison between mucinous adenocarcinoma and tubular adenocarcinoma.**

Histological	Muc: n = 17	Tub: n = 7	P value
Age at cancer diagnosis	64	62	.070
ADC mean ( $\times 10^{-3}$ mm <sup>2</sup> /s)	1.88	1.39	.005
CD	3	3	
Tumor depth	Tis-T1-T2	T3-T4	P value
Age at cancer diagnosis	58	67	.760
ADC mean ( $\times 10^{-3}$ mm <sup>2</sup> /s)	1.62	2.01	.020

ADC = apparent diffusion coefficient, CD = Crohn disease, Muc = mucinous adenocarcinoma, Tub = tubular adenocarcinoma.



**Figure 2.** ROC analysis of ADC values to determine the tumor histopathological type (left) and depth (right). ADC = apparent diffusion coefficient, AUC = area under the curve, CI = confidence interval, DWI-ROI = diffusion-weighted imaging-region of interest, ROC = receiver operating characteristic.

There are some reports on the effects of chemotherapy and pathological type of colon cancer. It has been reported that mucinous carcinoma has a poor response to chemotherapy.<sup>[6]</sup> It was reported that mucinous, colon, and rectal carcinoma showed poor response to 5-fluorouracil in 135 patients.<sup>[6,9]</sup> In a study comparing 49 patients with mucinous colorectal carcinoma to 206 patients with non-mucinous colorectal carcinoma, those with mucinous colorectal carcinoma showed poor response to irinotecan and/or oxaliplatin and had poor prognoses.<sup>[10]</sup> This study suggested that treatment response may be poor in patients with mucous carcinoma. In 1 review article, the utility of chemoradiotherapy was unclear.<sup>[17]</sup> However, histological type determination may become important in selecting the treatment strategy for anal fistula cancer, especially chemotherapy.

MRI is typically used in the imaging diagnosis of anal fistula cancer; in particular, DWI shows the tumor with high signal intensity. Furthermore, the ADC value is a parameter that can be used in clinical practice as a quantitative imaging biomarker.<sup>[18]</sup> In the present study, the difference in ADC values between mucinous and tubular adenocarcinomas reflects the pathological differences between these 2 types of tumor. Therefore, preoperative MRI is necessary, and the ADC value may suggest the histopathological diagnosis. In this study, non-contrast-enhanced MRI was evaluated. Based on the pathological findings at our hospital, the histological difference between mucinous

and tubular adenocarcinomas is that the former type tends to be edematous and with more stroma than the latter because of more mucus leaking into the stroma. In addition, mucinous carcinomas tend to have a sparse cell density due to the large amount of interstitium and may have fewer blood vessels than tubular adenocarcinomas. In the future, contrast-enhanced MRI may provide useful additional information for the histopathological diagnosis of anal fistula cancers.

This study has several limitations. First, the number of cases of anal fistula cancer was small because it is a rare disease arising from a fistula tract. Second, the study was retrospective, thus patient selection bias cannot be excluded. Third, it is difficult to completely define the area of anal fistula cancer compared with pathological findings on preoperative MRI images. Further studies are needed to increase the number of cases and examine the results in a multicenter setting.

**5. Conclusion**

The ADC values in preoperative anal MR images could distinguish the histopathological types of mucinous and tubular adenocarcinoma in an anal fistula cancer. Also, the different ADC values between Tis-T1-T2 and T3-T4 groups could help predict the classification of progression. Therefore, these results may provide useful information to decide the treatment strategy for these patients.



## Author contributions

**Conceptualization:** Shinji Yamamoto, Tetsuro Yamana.

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**Project administration:** Yukinori Okada.

**Supervision:** Yukinori Okada.

**Writing – original draft:** Shinji Yamamoto.

**Writing – review & editing:** Shinji Yamamoto, Tetsuro Yamana.

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