

Evaluation of malignancy in gallbladder tumors using the apparent diffusion coefficient obtained by diffusion-weighted MRI

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Abstract. The utility of the apparent diffusion coefficient (ADC) of diffusion-weighted image (DWI) magnetic resonance imaging was examined for evaluating malignancy and prognosis in gallbladder tumors. A total of 63 patients (benign tumors, n=33; cancer, n=30) were included after surgical resection for gallbladder tumors, and their mean ADC values by DWI were obtained. Cases of advanced gallbladder cancer (n=25) were divided into ADC^{High} and ADC^{Low} groups, and clinicopathological factors were compared. In 63 cases, ADC values in advanced gallbladder cancer were significantly lower compared with benign tumors and non-advanced gallbladder cancer ($P<0.05$), and ADC values in early gallbladder cancer were also significantly lower compared with benign tumors ($P<0.05$). In 25 advanced gallbladder cancer cases, the ADC^{Low} group tended to have a higher rate of advanced stage disease ($P=0.09$). Disease-free survival and overall survival (OS) of the ADC^{Low} group were worse compared with the ADC^{High} group ($P<0.01$). In the multivariate analysis of OS, poor differentiation and low ADC value were independent prognostic factors. ADC values may be useful for evaluating tumor malignancies in gallbladder tumors.

Introduction

Gallbladder cancer is a frequent malignant tumor of the biliary tract and shows a poor prognosis (1). It is a highly aggressive malignancy that is hard to diagnose and has few therapeutic options, with a 5-10% 5-year overall survival (OS) rate (2,3). In gallbladder cancer, cases diagnosed at the same tumor stage sometimes show different prognoses because of its heterogeneity (4). Additionally, distinguishing benign tumors from malignant tumors is difficult by conventional

imaging modalities (5). Therefore, accurate and early imaging diagnoses are necessary for selecting appropriate therapy and improving prognosis.

Although ultrasonography is considered one of the most reliable imaging modalities for evaluating gallbladder disease, it is hard to diagnose early lesions because of its low specificity and sensitivity (6). Morphological evaluation using computed tomography (CT) is also widely used. However, it is hard to distinguish gallbladder cancer from other benign tumors such as chronic cholecystitis (7). In recent years, diffusion-weighted imaging (DWI) of magnetic resonance imaging (MRI) has shown radical improvement in the detection of malignant tumors (8). DWI is a functional MRI technique that can assess diffusion of water molecules and evaluate the pathological condition of organs and tissue at a high scan speed without a contrast agent. A quantitative assessment of diffusion characteristics can be presented by apparent diffusion coefficient (ADC) values (9); they are decreased in areas in which diffusion is restricted, such as in tissue with high cellularity or rich stroma. Previously, it has been reported that ADC values could estimate the characteristics of various malignancies (10,11). Our previous study also demonstrated that ADC values can estimate the prognosis of intrahepatic cholangiocarcinoma (12). Previously, DWI was shown to support the diagnosis of gallbladder malignancy and can also distinguish gallbladder cancers from benign tumors in gallbladder (6), while the ADC value can estimate the histological grade of primary gallbladder carcinoma (13).

The present study examined the utility of ADC values in the evaluation of malignancies and in the prognostic prediction of gallbladder tumors.

Materials and methods

Patients and MRI imaging. In the present study, a total of 63 patients (44 female and 19 male patients; median age, 62 years; age range, 25-91 years) who underwent surgical resection for gallbladder tumors at the Department of Surgery, Tokushima University Hospital, between January 2011 and December 2023 were enrolled. The patients that were included: i) Underwent DWI of MRI within 1 month before surgical resection; ii) showed no previous treatment before surgical resection, and no extrahepatic metastasis; and iii) had

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a gallbladder tumor confirmed pathologically. Cases of non-curative resection (R2) and patients that underwent neoadjuvant chemotherapy were not included in the present study. Regarding gallbladder cancer, morphological and pathological characteristics and the Japanese Tumor-Node-Metastasis stage were assessed according to the guidelines of the Japanese Society of Biliary Surgery (14).

MR images were obtained with 1.5-T superconducting units (Signa HD/Explorer; GE Healthcare) using 8-channel phased-array coil. Fast spin-echo T2-weighted images and DWI ($b=0, 20, 800 \text{ s/mm}^2$) were obtained. Using ADC maps on Synapse Vincent (ver. 6.8; Fujifilm Healthcare), the mean ADC values ($\times 10^{-3} \text{ mm}^2/\text{sec}$) of tumors were calculated in regions of interest with manual tracing (12). Synapse Vincent can obtain the maximum, minimum and mean values in free-form green lines automatically (Fig. 1). In the present study, mean ADC values were used as previously reported (15), and cases of gallbladder cancer were divided into non-advanced gallbladder cancer, whereby the tumor depth was the mucosa or muscular layer, and advanced gallbladder cancer, in which the tumor depth was deeper than the muscular layer. In advanced gallbladder cancer ($n=25$), patients were divided into 2 groups using the ADC value: An ADC^{High} group ($n=15$) and an ADC^{Low} group ($n=10$). Using receiver operating characteristic analysis, of which the endpoint is cancer death, the cut-off value of $1.2 \times 10^{-3} \text{ mm}^2/\text{sec}$ was defined (area under the curve: 0.75, sensitivity: 72.7%, specificity: 85.7%, Fig. 2). The present study was approved by the Institutional Review Board of the Tokushima University Hospital (approval no. 3977-2; Tokushima, Japan). The requirement for written consent was waived for the present study by the ethical approval committee.

Statistical analysis. The Fisher's exact test was used to compare the patients' backgrounds of the two groups. For multiple comparisons, the Kruskal-Wallis test and Steel-Dwass post hoc test were used. Disease-free survival (DFS) and OS curves were generated using the Kaplan-Meier method and differences were evaluated by the log-rank test. Cox proportional hazards model was used for multivariate survival analysis. $P < 0.05$ was considered to indicate a statistically significant difference, and all statistical analyses were performed by JMP v.8.0.1 (SAS Institute Inc.).

Results

ADC value of gallbladder tumors. In the present study, there were 33 benign tumor cases, 5 non-advanced gallbladder cancers, and 25 advanced gallbladder cases. Patients' characteristics in benign tumors and gallbladder cancers are presented in Tables I and II. Images of representative cases of tumor are revealed in Fig. 3. ADC values of benign tumors and gallbladder cancer are included in Tables I and II. The mean ADC value was $2.72 \times 10^{-3} \text{ mm}^2/\text{sec}$ in benign tumors, $1.88 \times 10^{-3} \text{ mm}^2/\text{sec}$ in non-advanced gallbladder cancer and $1.36 \times 10^{-3} \text{ mm}^2/\text{sec}$ in advanced gallbladder cancer. ADC values in the three groups are demonstrated in Fig. 4. ADC values in advanced gallbladder cancer were significantly lower compared with benign tumors and non-advanced gallbladder cancer ($P < 0.05$). Furthermore, ADC values in early gallbladder

Table I. Patients' characteristics in benign gallbladder tumors.

Variable	n=33
Age, years	52 $\pm$ 13
Sex (male/female)	10/23
Diagnosis (adenoma/hyperplastic polyp/cholesterol polyp)	8/9/16
Tumor size (mm)	10.5 $\pm$ 3.9
Tumor number (single/multiple)	14/19
ADC value ($\times 10^{-3} \text{ mm}^2/\text{sec}$)	2.72 $\pm$ 0.35

ADC, apparent diffusion coefficient.

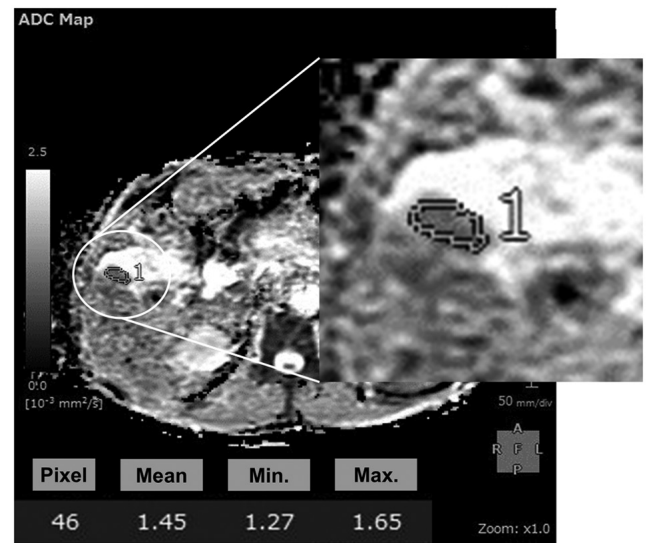


Figure 1. Calculation of ADC values using Synapse Vincent with manual tracing. Mean, minimum and maximum values were calculated, as shown automatically by free-form green lines. ADC, apparent diffusion coefficient.

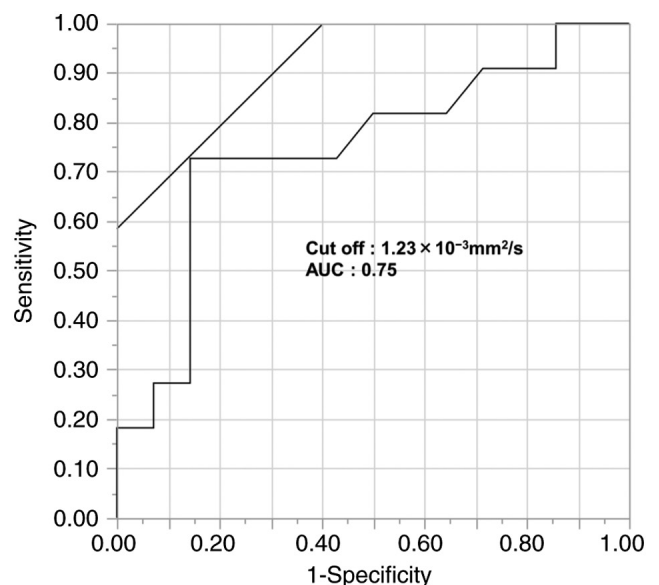


Figure 2. Receiver operating characteristic analysis to determine the proper cut-off value of mean apparent diffusion coefficient values. Cut-off value was $1.23 \times 10^{-3} \text{ mm}^2/\text{sec}$ with an AUC of 0.75. AUC, area under the curve.

Table II. Patients' characteristics in gallbladder carcinoma.

Case	Age/ Sex	Tumor progression	Lymph node metastasis	Differentiation	Adjuvant chemotherapy	Vessel invasion	Recurrence	ADC value ($\times 10^{-3} \text{mm}^2/\text{sec}$)
1	59/F	Advanced	-	Por	+	+	+	1.22
2	60/F	Advanced	+	Tub	+	-	+	1.17
3	67/F	Advanced	+	Tub	+	+	-	1.44
4	72/F	Advanced	-	Tub	+	+	+	1.04
5	58/F	Advanced	-	Tub	-	+	+	0.89
6	61/F	Advanced	+	Tub	+	+	+	1.3
7	79/F	Advanced	+	Tub	-	+	+	1.56
8	76/F	Advanced	+	Tub	+	+	+	1.05
9	74/F	Advanced	-	Tub	-	-	-	1.63
10	68/M	Advanced	+	Tub	+	+	+	1.17
11	69/M	Advanced	+	Tub	+	+	+	1.77
12	59/M	Advanced	-	Tub	+	+	-	1.1
13	67/F	Advanced	-	Pap	-	-	-	1.92
14	90/M	Advanced	-	Pap	-	+	-	1.51
15	88/F	Advanced	+	Pap	-	+	-	1.56
16	88/F	Advanced	+	Tub	-	+	+	1.46
17	70/F	Advanced	+	Por	-	+	+	1.12
18	72/M	Advanced	+	Por	+	+	+	0.58
19	58/M	Advanced	-	Tub	-	+	-	1.38
20	91/M	Advanced	-	Pap	-	+	+	1.88
21	70/M	Advanced	-	Tub	-	+	-	1.45
22	76/F	Advanced	-	Pap	-	+	-	1.67
23	67/M	Advanced	-	Por	+	+	+	1.23
24	63/F	Advanced	-	Tub	-	-	-	1.49
25	62/F	Advanced	-	Tub	-	+	-	1.46
26	68/F	Non-advanced	-	Pap	-	-	-	1.72
27	84/F	Non-advanced	-	Tub	-	-	-	1.33
28	71/F	Non-advanced	-	Pap	-	-	-	2.08
29	68/F	Non-advanced	-	Tub	-	-	-	2.14
30	70/F	Non-advanced	-	Pap	-	-	-	2.13

ADC, apparent diffusion coefficient; Tub, tubular; Por, poorly differentiated; Pap, papillary; F, female; M, male.

Table III. Patients' characteristics in the ADC low and high groups.

Variable	Expression level of ADC		P-value
	Low (n=10)	High (n=15)	
Age (<70 / >70 years)	5/5	8/7	>0.99
Sex (male/female)	7/3	9/6	0.69
CEA (<5 / >5 ng/ml)	7/3	12/3	0.65
CA19-9 (<37 / >37 U/ml)	3/7	7/8	0.68
LN metastasis (-/+)	4/6	10/5	0.24
Stage (I/II/III)	0/2/8	0/8/7	0.21
Differentiation (tub/others)	7/3	14/1	0.27
Vessel invasion (-/+)	1/9	3/12	0.63
Adjuvant chemotherapy (-/+)	3/7	11/4	0.049

ADC, apparent diffusion coefficient; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; LN, lymph node; tub, tubular.

cancer were also significantly lower compared with benign tumors ($P<0.05$).

Evaluation of malignancy with ADC in advanced gallbladder cancer. The backgrounds of patients with advanced gallbladder cancer are revealed in Table III. The ADC^{Low} group tended to have a higher rate of advanced stage disease ($P=0.21$), and a significantly higher rate of adjuvant chemotherapy compared with the ADC^{High} group ($P<0.05$). Regarding OS, significantly worse prognosis was shown in the ADC^{Low} group compared with the ADC^{High} group ($P<0.01$) (Fig. 5). The univariate and multivariate analyses of OS are shown in Table IV. Poor differentiation and low ADC value were identified as independent prognostic factors. Regarding DFS, the ADC^{Low} group also showed a significantly worse prognosis than the ADC^{High} group ($P<0.01$) (Fig. 6). The univariate and multivariate analyses of DFS are demonstrated in Table V. Low ADC value was identified as an independent prognostic factor. Furthermore, the ADC^{Low} group revealed a higher rate of extra-hepatic recurrence compared with ADC^{High} group (Fig. 7).

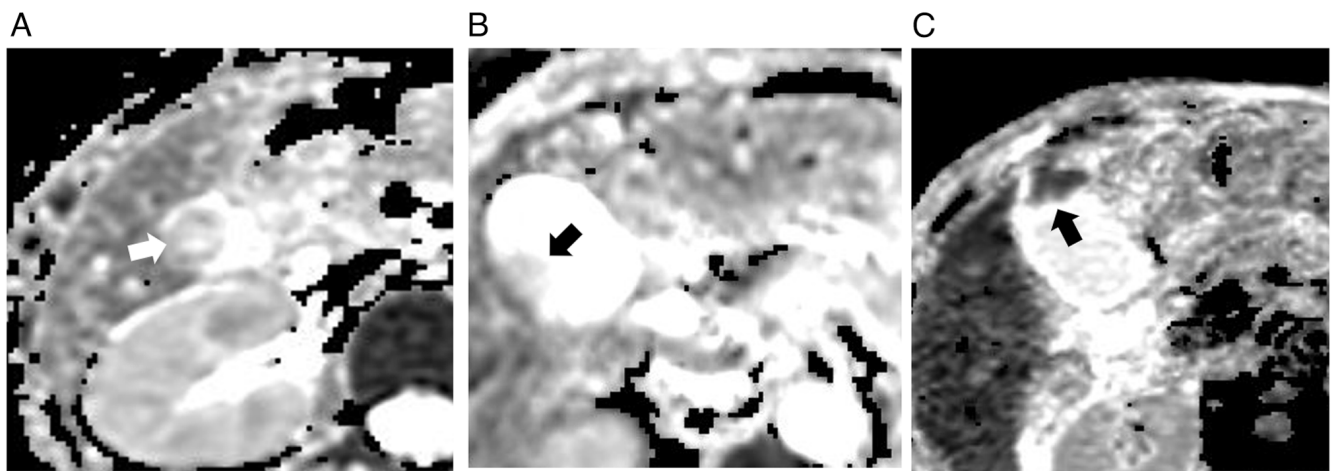


Figure 3. Representative cases of tumor. (A) Adenomyomatosis, (B) non-advanced cancer, and (C) advanced cancer. Mean apparent diffusion coefficient values were 2.72×10^{-3} , 1.88×10^{-3} and 1.36×10^{-3} mm²/sec, respectively.

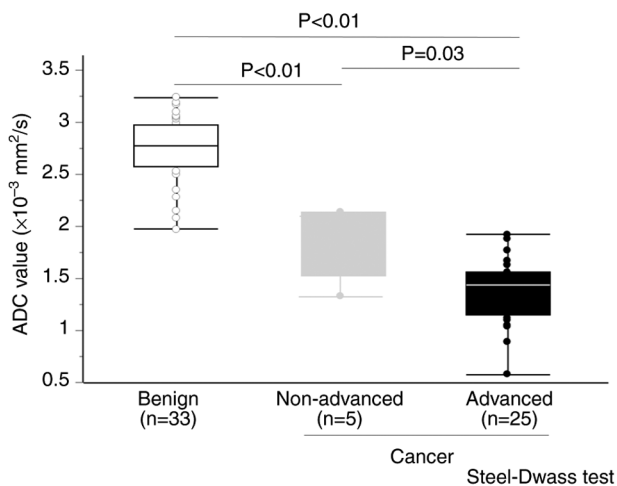


Figure 4. ADC values of the three groups. ADC values in advanced gallbladder cancer were significantly lower compared with benign tumors and non-advanced gallbladder cancer ($P<0.05$). Furthermore, ADC values in early gallbladder cancer were also significantly lower compared with benign tumors ($P<0.05$). Steel-Dwass test was used for multiple comparisons. ADC, apparent diffusion coefficient; NS, no significance.

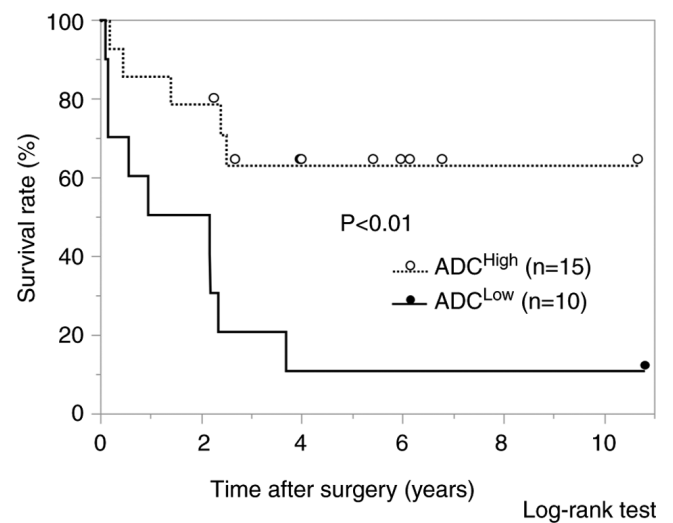


Figure 6. Disease-free survival rate of the two groups. Significantly worse prognosis was shown in the ADC^{Low} group compared with the ADC^{High} group ($P<0.01$). Log-rank test was used. ADC, apparent diffusion coefficient.

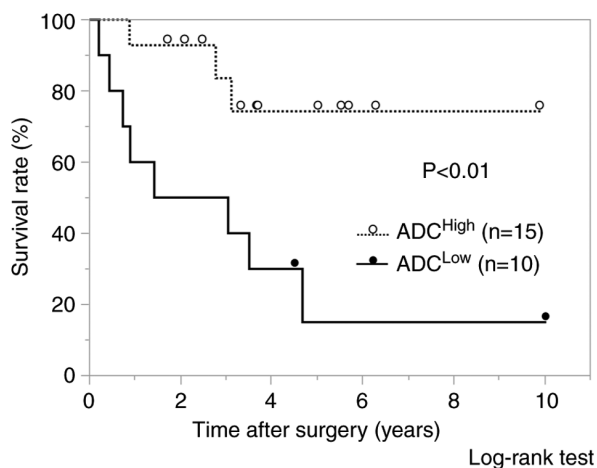


Figure 5. Overall survival rate of the two groups. Significantly worse prognosis was shown in the ADC^{Low} group compared with the ADC^{High} group ($P<0.01$). Log-rank test was used. ADC, apparent diffusion coefficient.

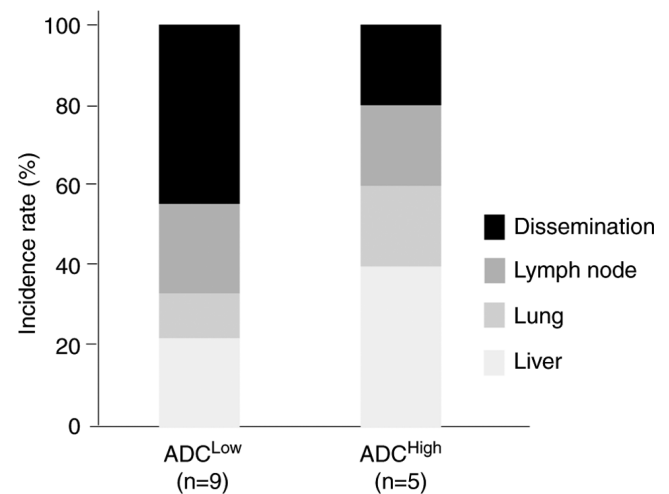


Figure 7. Recurrence pattern of the ADC^{Low} and ADC^{High} groups. The ADC^{Low} group showed a higher rate of extra-hepatic recurrence compared with the ADC^{High} group. ADC, apparent diffusion coefficient.

Table IV. Multivariate analysis for overall survival.

Variable	Univariate	Multivariate	
	P-value	HR (95% CI)	P-value
Age [≥70 (Ref: <70 years)]	0.70	0.66 (0.05-7.98)	0.75
Sex [male (Ref: female)]	0.93	0.71 (0.09-5.44)	0.74
CEA [≥5 (Ref: <5 ng/ml)]	0.10	5.16 (0.46-57.5)	0.18
CA19-9 [≥37 (Ref: <37 U/ml)]	0.53	1.30 (0.13-13.5)	0.82
LN metastasis [+ (Ref: -)]	0.04	3.91 (0.34-44.3)	0.27
Differentiation [others (Ref: tub)]	<0.01	19.3 (1.40-266.9)	0.03
Vessel invasion [+ (Ref: -)]	0.28	4.73 (0.29-78.0)	0.28
Adjuvant chemotherapy [+ (Ref: -)]	0.32	0.09 (0.004-1.60)	0.10
ADC [low (Ref: high)]	<0.01	9.51 (1.38-65.4)	0.02

HR, hazard ratio; CI, confidence interval; Ref, reference; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; LN, lymph node; tub, tubular; ADC, apparent diffusion coefficient.

Table V. Multivariate analysis for disease-free survival.

Variable	Univariate	Multivariate	
	P-value	HR (95% CI)	P-value
Age [≥70 (Ref: <70 years)]	0.70	0.76 (0.17-3.65)	0.78
Sex [male (Ref: female)]	0.74	0.95 (0.18-4.99)	0.95
CEA [≥5 (Ref: <5 ng/ml)]	0.18	2.84 (0.39-20.7)	0.30
CA19-9 [≥37 (Ref: <37 U/ml)]	0.47	1.91 (0.23-15.9)	0.55
LN metastasis [+ (Ref: -)]	0.04	2.41 (0.51-11.4)	0.27
Differentiation [others (Ref: tub)]	<0.01	3.62 (0.63-20.9)	0.15
Vessel invasion [+ (Ref: -)]	0.18	2.99 (0.32-28.2)	0.34
Adjuvant chemotherapy [+ (Ref: -)]	0.11	0.25 (0.03-2.00)	0.19
ADC [low (Ref: high)]	<0.01	9.06 (1.44-57.1)	0.02

HR, hazard ratio; CI, confidence interval; Ref, reference; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; LN, lymph node; tub, tubular; ADC, apparent diffusion coefficient.

Table VI. Summary of studies using the ADC values in diagnosing gallbladder tumors.

First author, year	ADC in malignant tumor	ADC in benign tumor	P-value, cut-off value	(Refs.)
Sugita <i>et al</i> , 2009	1.28±0.41	1.92±0.21	<0.01	(22)
Irie <i>et al</i> , 2011	1.34±0.50	2.26±0.44	0.00016	(23)
Ogawa <i>et al</i> , 2012	1.83±0.69	2.60±0.54	0.001	(24)
Solak <i>et al</i> , 2012	0.98±0.13	1.96±0.26	<0.01, 0.86	(25)
Kim <i>et al</i> , 2013	1.46±0.45	2.16±0.56	<0.0001	(26)
Lee <i>et al</i> , 2014	1.04±0.38	2.20±0.72	<0.001	(27)
Kyung <i>et al</i> , 2016	1.041	2.039	<0.001	(28)
Kitazume <i>et al</i> , 2016	1.06±0.37	1.85±0.32	<0.001	(7)
Suliman <i>et al</i> , 2021	1.27	1.62	0.07	(29)

ADC, apparent diffusion coefficient.

Discussion

In the present study, the usefulness of ADC in the estimation of malignancy and in prognostic prediction was demonstrated. First, ADC values in malignant and benign gallbladder tumors were investigated. ADC values in advanced gallbladder cancer were significantly lower than those in benign tumors and non-advanced gallbladder cancer, and ADC values in non-advanced gallbladder cancer were significantly lower than those in benign tumors. Differentiation of early malignant and benign gallbladder tumors using conventional CT and MRI has been reported to be difficult and challenging (16-18). It is hard to diagnose gallbladder carcinoma when it reveals wall thickness because it is more common than the wall thickness of inflamed gallbladder. Furthermore, although polypoid tumors >1 cm in diameter have the potential to be cancer, benign gallbladder tumors >1 cm are frequent (19,20). The present study confirmed that non-advanced gallbladder cancer could be distinguished from benign tumors using ADC values. Therefore, when polypoid lesions show relatively low ADC values and are suspicious for early gallbladder cancer, laparoscopic radical cholecystectomy may be considered (21).

A small number of studies (7,22-29) have used ADC values to differentiate gallbladder carcinoma from benign tumors (Table VI). These studies stated that ADC values are useful for distinguishing gallbladder carcinoma and benign tumors. Lee *et al* (27) demonstrated sensitivity, specificity, positive predictive value and negative predictive value of 97.2, 92.2, 83.3 and 98.8%, respectively. However, these cut-off points vary between studies, which limits their clinical validity. Kitazume *et al* (7) revealed that the lesion to spinal cord ratio was more accurate than ADC. Sulieman *et al* (29) showed that the P-value between gallbladder carcinoma and benign tumor was 0.07, although the P-value of b800/b0 ratio was <0.01. This correction of ADC value with other lesions using the b-value ratio may reduce this validity.

Next, malignancy in advanced gallbladder cancer using ADC values was estimated. A previous study reported that tumor differentiation was inversely related to the ADC value (13). It was previously reported that low ADC value is associated with aggressive tumor types and high HIF-1 α expression, which accelerates tumor malignancy in intrahepatic cholangiocarcinoma (12). Furthermore, Min *et al* (15) showed that the low ADC value in gallbladder cancer was associated with poor differentiation, T stage, lymph node metastasis and progression stage. In the present study, the ADC^{Low} group tended to have a higher rate of advanced stage, which represented tumor aggressiveness. Min *et al* (15) also confirmed that low ADC values could estimate long-term DFS. The current study revealed a significant difference in OS, not only in DFS, and the ADC^{Low} group showed more extrahepatic distant recurrence compared with the ADC^{High} group, indicating an aggressive recurrence pattern.

The present study has some limitations. First, selection bias could exist because only patients with gallbladder tumors who underwent MRI were retrospectively analyzed. Second, patients in the present study underwent treatment at a single center, and the number of patients was small. Statistical size calculations were not conducted, and sample size of the present study gave post hoc powers of 22%. Therefore, further analysis

in a larger, prospectively collected population is necessary to confirm these results.

In conclusion, ADC values from DWI-MRI may estimate the malignancy of gallbladder tumors and predict the prognosis of patients with advanced gallbladder cancer.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YM, MS and SY designed the study. CN, SY, HT, YW, YS, TI and TN contributed to collection of the data. SY and CN wrote the main manuscript text, confirmed the authenticity of all the raw data and prepared all figures. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Tokushima University Hospital (approval no. 3977-2; Tokushima, Japan). An information disclosure statement was presented in the homepage of the institute website for opt-out, and the requirement for informed consent was waived.

Patient consent for publication

An information disclosure statement was shown in the homepage of Tokushima University Hospital website for opt-out; The manuscript and images are published and freely available.

Competing interests

The authors declare that they have no competing interests.

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