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The role of diffusion-weighted examination in non-polyploid gallbladder malignancies: A preliminary study

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Background/aims: *The aim of the present study was to investigate the diagnostic value of diffusion-weighted magnetic resonance imaging in gallbladder malignancies, which are typically diagnosed during surgery because the radiologic findings are similar to those of cholecystitis-caused diffuse thickening of the gallbladder wall.* ***Materials and Methods:*** *Seven patients with gallbladder malignancies and nine patients with benign gallbladder pathology were included in this study. In one of the patients with a malignancy, a lesion was determined on the porcelain gallbladder; in another patient, acute myeloblastic leukemia had infiltrated the gallbladder, causing the diffuse wall thickening. Five subjects had a primary malignant gallbladder. The view of the bladder wall was evaluated visually in increasing b values. Apparent diffusion coefficient measurements were obtained from at least three sites of the bladder wall in each patient, and the results of the measurements were analyzed after comparing the malignant and benign groups. In the malignant group, the results of the radiological outcomes were compared with histological examinations. In the benign group, cholecystitis was diagnosed by observing normalization of the bladder wall thickening via surgery or medical treatment.* ***Results:*** *There was a statistically significant difference in apparent diffusion coefficient levels between the malignant group, which caused diffuse thickening of the gallbladder wall, and the benign group (Student t test, p<0.01).* ***Conclusions:*** *According to this preliminary study, observation of distinct brightness of the gallbladder wall in diffusion-weighted examination with a high b value is a significant finding in terms of diffuse gallbladder malignancy. A value below the 0.86 mm²/sn cut-off was significant for malignancy in apparent diffusion coefficient mapping.*

Key words: Cancer, gallbladder, diffusion-weighted magnetic resonance imaging, cholecystitis

Non-polipoid safra kesesi tümörlerinde difüzyon ağırlıklı incelemenin rolü: Preliminer çalışma

Amaç: *Bu çalışmanın amacı safra kesesinde diffüz duvar kalınlaşmasına yol açan, kolesistitle benzer radyolojik bulgular oluşturduğu için çoğu zaman operasyon sırasında tanısı konulan diffüz safra kesesi malignitelerinde diffüzyon ağırlıklı manyetik rezonans görüntülemenin tanı değerini araştırmaktır.* ***Gereç ve Yöntem:*** *Yedi malign, 9 benign kese patolojili hastayı değerlendirdik. Maligniteli hastaların birinde lezyon porselen safra kesesi üzerine eklenmiştir, bir hastada akut myeloblastik lösemi'nin safra kesesinde diffüz malign infiltrasyona yol açtığı saptanmıştır. Beş olgu primer kese malignitesidir. Artan b değerlerinde kese duvarının görünümü görsel olarak değerlendirilmiştir. Kese duvarından en az 3 lokalizasyondan görünür difüzyon katsayısı ölçümleri alınmış, elde olunan ölçümler malign ve benign gruplarda karşılaştırılıp sonuçlar analiz edilmiştir. Olguların radyoloji sonuçları malign grupta histopatolojik incelemeyle korele edilmiştir. Kolesititli hastalarda operasyon sonucuyla veya medikal tedaviyle kese duvar kalınlığının normale döndüğü gözlenerek korelasyon sağlanmıştır.* ***Bulgular:*** *Safra kesesinde diffüz duvar kalınlaşması oluşturan malign grupla benign grup arasındaki görünür difüzyon katsayısı değerleri arasında istatiksel olarak anlamlı farklılık görülmektedir (student t testi, p<0.01).* ***Sonuç:*** *Yüksek b değerlikli diffüzyon ağırlıklı incelemede safra kesesinde duvar parlaklaşması, bizim bu preliminer çalışmamıza göre diffüz kese malignitesi açısından anlamlı bulgudur. Görünür difüzyon katsayısı haritalamada 0.86 mm²/sn cut-off değerinin altındaki değerler malignite için anlamlıdır.*

Anahtar kelimeler: Kanser, safra kesesi, diffüzyon ağırlıklı manyetik rezonans görüntüleme, kolesistit

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INTRODUCTION

Gallbladder carcinomas (GBC) are very rare malignancies. The incidence increases with age and is more common in women (1). The overall incidence is 2.9% of all cancer cases and 31.8% of all malignant tumors of the gastrointestinal tract. The male to female ratio is 1:2.64 (2). An association with gallstone increased the risk of GBC from 4 to 7 times more than in those without gallstone. Histologically, the most frequently seen carcinoma is adenocarcinoma, followed by epidermoid carcinoma. Regardless of its histology, these malignancies are mostly inoperable. Lesions present as tumoral masses filled 50-60% with gallbladder stones at the time of diagnosis because they demonstrate no early diagnostic findings, and symptoms are usually masked by chronic cholecystitis. The easily diagnosable mass (barely visible with only 15-20% ratio) with polyploid projection distinguished itself as 35-40% diffuse wall thickening. Diffuse thickening of the wall is often mistaken as acute or chronic cholecystitis and thus complicates the diagnosis (2-4). Ultrasonography (US), computerized tomography (CT) and magnetic resonance (MR) can show diffuse thickening of the gallbladder wall. However, these techniques cannot distinguish malignancy from situations such as acute or chronic cholecystitis or adenomyomatosis (4,5). The aim of this study was to investigate the diagnostic value of the obtained qualitative and quantitative results by diffusion-weighted MR examinations in the pathologies that cause diffuse thickening of the gallbladder wall.

MATERIALS AND METHODS

Seven subjects diagnosed histopathologically with diffuse gallbladder malignancies in our hospital between January and September 2011 and nine patients with cholecystitis were included in this study. Eleven subjects were female and five were male, and the mean age of all subjects was 56.2 years. The malignant group included only one male. All subjects underwent US (Siemens Acuson Antares) examination before MR, and three subjects underwent abdominal CT exam (Siemens Somatom Sensation, Dual Source Technology). Following these exams, the subjects who displayed diffuse thickening of the gallbladder wall were directed to MR. US showed the view of the diffuse thickened gallbladder wall in patients in the benign group. The patients with obvious pericholecystic fluid were excluded from the study.

MR examinations were made with a 1.5 T superconductive device (Siemens MAGNETOM Espree 1.5T) using body coil. Intravenous (IV) contrast was performed during MR examinations. First, guide gradient echo images with coronal T1-weighted sections were taken (TR/TE 100-160/1.5, flip angle 90°) to determine stones in the gallbladder. Afterwards, images that had high anatomic resolution HASTE (single shot TSE/FSE), T1 and axial T2-weighted fat-suppression (TR/TE 3600/87, flip angle 150°) were obtained. The thickening of sections in the axial T2 images was considered to be the same as diffusion-weighted images (DWI). Echoplanar DWIs were obtained with a breath hold-respirator triggered technique and a fat-suppressed technique with axial view (TR/TE 5000/80, matrix 192x156, thickness: 6 mm, gap: 1.8 mm). Images, including the view from isotropic b 800 to b 0 as well as bladder lodge, were sent to the work-station to scan for lesions (Leonardo, Siemens Syngo Explorer Workstation, Germany). The regions with clear thickening and irregular areas of the wall were scanned in T2-weighted axial sections with guidance from conventional MR sequences and US. The measurement was made with the circular ROI (region of interest) located on the lesion from the projection of apparent diffusion coefficient (ADC) mapping of hyperintense localization points in the images with a high b value. The diameters of the ROI ranged from 3-9 mm in the cholecystitis group and 3-10 mm in the group with tumors. At least three images were taken from each region of suspect during diffusion scanning. At least three regions were evaluated in each image, and the mean was calculated from these nine measurements obtained from each patient. Chi-square and Student-t tests were used to evaluate whether there were differences in age distribution and ADC results between the benign and malignant groups.

RESULTS

All patients with gallbladder tumors underwent surgery. Their diagnoses consisted of adenocarcinoma in five patients and epidermoid carcinoma in one patient. In the group with malignancies, a lesion was determined on the porcelain gallbladder in one patient (Figures 1A-C). In another patient, it was reported that acute myeloid leukemia caused the diffuse wall thickening by infiltrating the gallbladder. Three of the five patients with adenocarcinoma with primary bladder malignan-

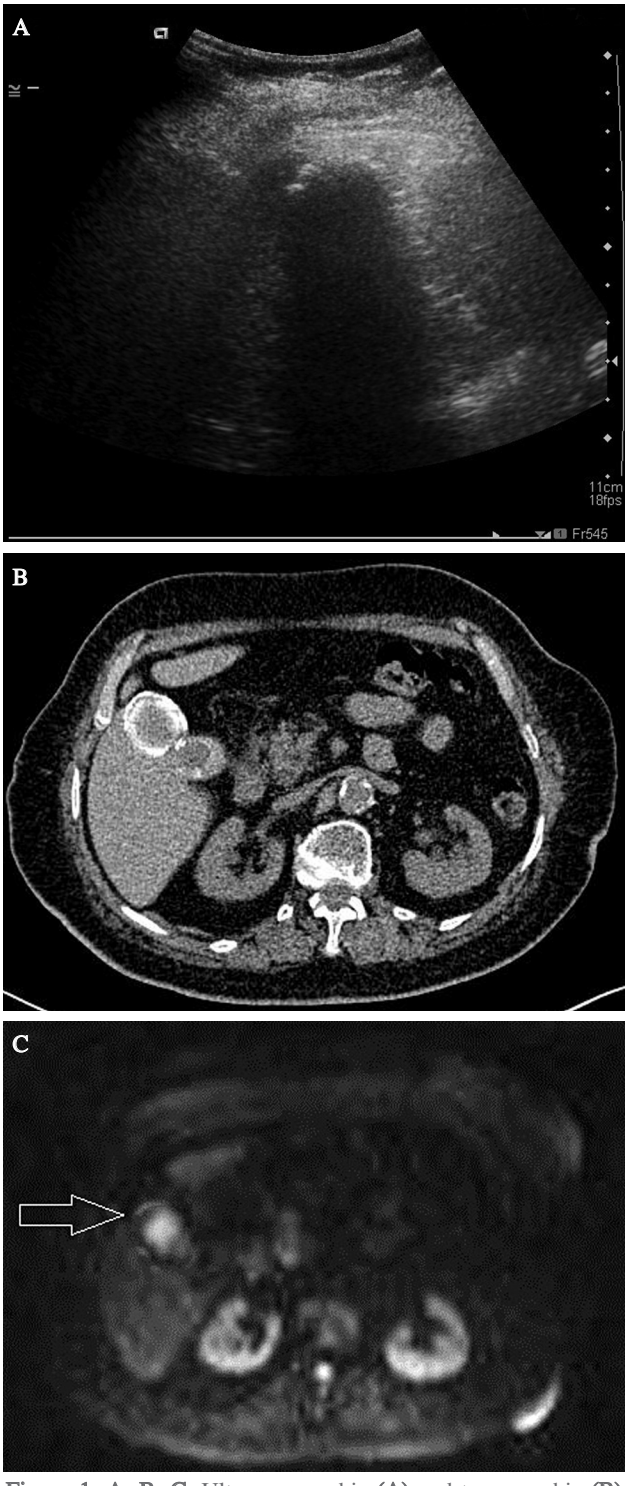

Figure 1. A, B, C. Ultrasonographic **(A)** and tomographic **(B)** view and diffusion-weighted (b800) image **(C)** of porcelain gallbladder. Note that the outer wall of the bladder has thin linear hyperintense line due tumoral hypercellularity (arrow).

cies had a histologic grade of 4, and the other two patients had a histologic grade of 2. There was intra-abdominal lymphatic metastasis in three patients and liver metastasis in two patients. In the patients with malignancies, it was difficult to determine malignancy from the routine scans. However, the gallbladder showed distinct brightness compared to the neighboring liver parenchyma in diffusion-weighted examination (b800). In these regions, diffusion restriction was observed in the ADC map (Figures 2A-F).

Six patients with cholecystitis underwent surgery. Inflammatory changes in the gallbladder were determined in these patients via histopathologic outcomes. Two patients had no malignancy or pathology other than a polyp accompanying inflammation. The diameter of the gallbladder normalized after medical treatment in three patients in the benign group. Gallbladder stones accompanied lesions in five patients in the malignant group and six patients in the benign group.

The mean ADC value in the patients with cholecystitis was found to be 1.96±0.26. The mean ADC value in the malignant group was found to be 0.98±0.13. ADC values in the patients with cholecystitis were significantly higher compared to the malignant group ($p<0.01$). The mean age of the patients with bladder malignancies was 69.4 years, while that of the cholecystitis group was 53 years. Results from statistical analysis showed that there was a statistically significant difference in age and ADC values between the benign and malignant groups ($p<0.01$). The gallbladder wall was repressed, and gained a non-signal like character in DWI with high b values in all patients with cholecystitis upon visual evaluation (Figure 3A, B, C). However, bright regions were observed within close configuration to the gallbladder in malignant lesions. Accordingly, carcinoma-cholecystitis in seven malignancies and nine benign lesions were correctly diagnosed by high b value images (sensitivity 78%, specificity 100%).

DISCUSSION

The technique of DWI is based on visualization of erratic and constant movement, due to heat, of the protons from water molecules (Brownian motion). It is a gold standard for early diagnosis of ischemic pathologies in the central nervous system (CNS) (6). Its use has recently been increased outside the CNS due to the development of echo planar visualization (7,8). The usage area has been expanding, especially because it provides qualitative and quantitative information for tumor diagnosis and evaluates the spread. To measure ADC values, one must allow for the qualitative evaluation in

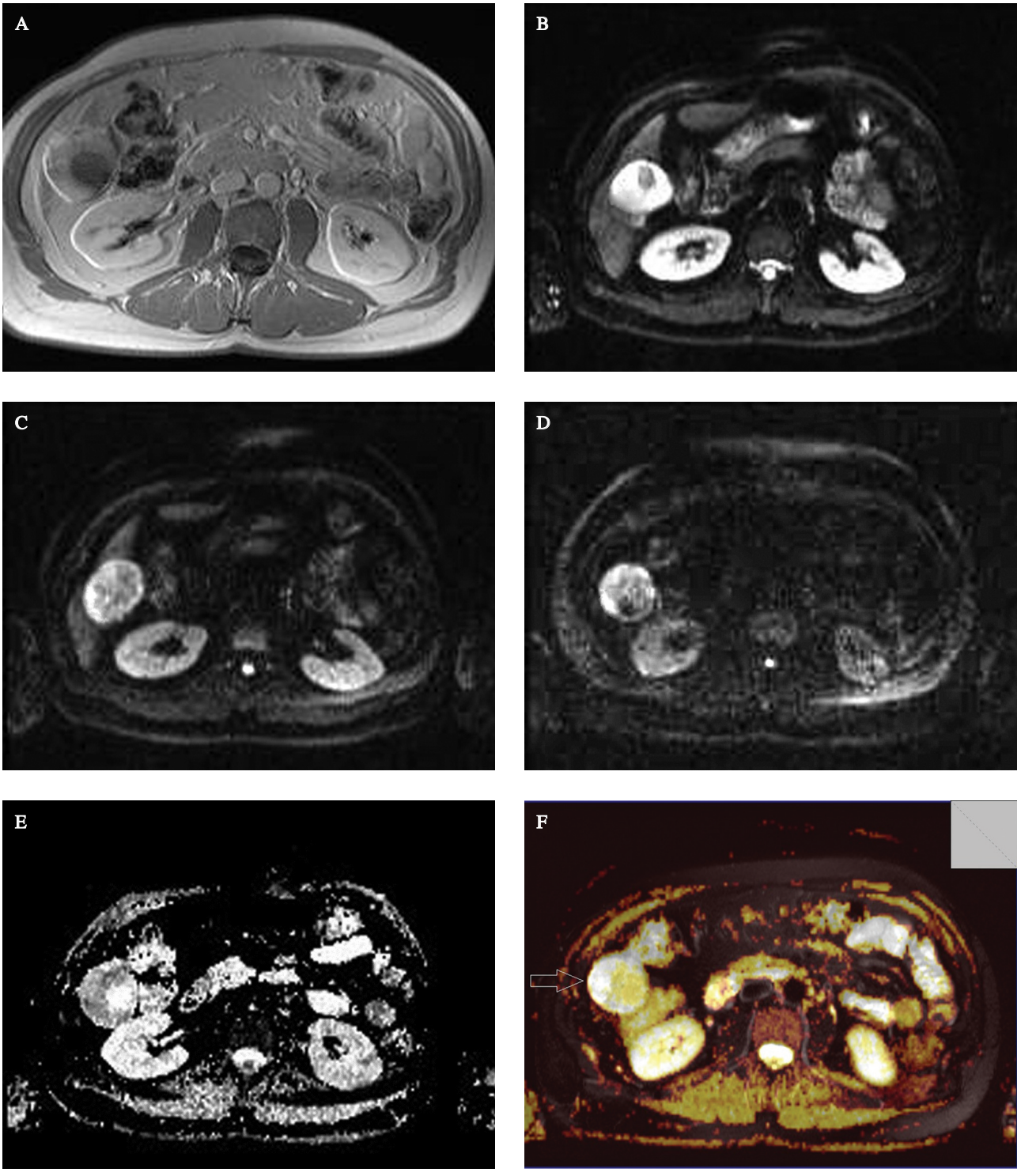

Figure 2. A, B, C, D, E, F. Postcontrast T1-weighted image. **(A)** Gallbladder wall is disordered in the patient with diffuse malignancy. The demilune shape hyperintensity on the wall of the bladder in diffusion-weighted sections (**B:** b0, **C:** b400, **D:** b800) is an indicator for hypercellularity-malignancy in this localization. In the ADC map, this area become hypointense and indicates tumoral hypercellularity **(E)** (ADC: 0.96±0.11). Corresponding color fusion (T2 and diffusion) image **(F)** shows gallbladder has white wall very similar to hypercellular renal parenchyma, and the lumen of the gallbladder is relatively hypointense (arrow).

DWIs to be made using different b values. ADC values tend to decrease due to increased tissue cellularity and cell density in malignant cells. Increased intracellular fluid due to edema suspends the cells from each other and decreases the cellularity of the tissue during inflammatory events. In this

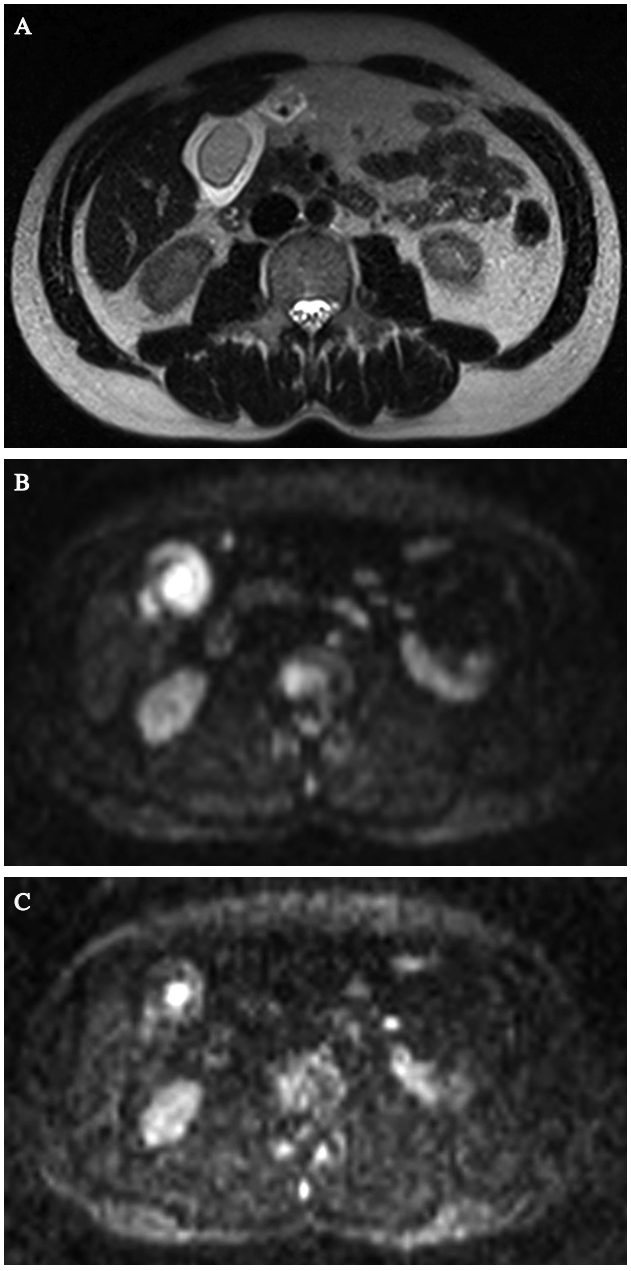

Figure 3. A, B, C. T2-weighted axial image shows diffuse wall thickening in the patient with cholecystitis. The lesion disappeared when the weight of diffusion was increased (ADC: 2.1±0.36).

case, the ADC value will be increased. The numbers of studies in the literature that have evaluated abnormal organ tumors with ADC results are increasing (9-11).

Qualitative evaluation is the visual evaluation of changes (12). In this study, qualitative evaluation was performed by observing the increased diffusion interval; in other words, by the increased b value on the signal in the images. In the visual evaluation, hyperintense areas in the sections with high b values from patients who were thought to have a carcinoma were determined (qualitatively), and after adding ADC values on these areas, these two groups were compared (quantitative evaluation).

There are many studies related especially to the qualitative evaluation that differentiates benign and malignant liver lesions (11). Increasingly, more studies have come into question related to the evaluations of colon and pancreatic tumors (9,10). Gallbladder malignancies are rare, progressive, and usually diagnosed at an inoperable stage (stage 4), and they carry a survival rate that is lower than 2% in five years. Therefore, early diagnosis is of the utmost importance (2-5).

Diffuse malignancies cannot be distinguished from cholecystitis in US and CT (13-14). Both the inflammation in the gallbladder and also the malignant lesions can capture contrast in routine MR scans (15,16). DWI scans, which are extremely easy to apply and interpret and can be done in a breath in-breath out duration without requiring contrast, can show hypercellular-tumoral regions when they are added to routine MR examinations (17). Sugita et al. (12) emphasized in their study that DAG is superior in displaying gallbladder tumors. In their study, seven of 15 patients with bladder malignancy had diffuse malignancies, and the diagnosis of these patients was made correctly.

This pilot study has some limitations. First, the study groups consisted of a limited number of subjects; the number of subjects needs to be increased in future studies, in addition to broadening the various pathologies of the patient groups. This especially should include subjects with xanthogranulomatous cholecystitis, which imitates gallbladder malignancy, as distinguishing between these two diagnoses is difficult (18). The second limitation was the retrospective nature of the study, which included patients who were known to have gallbladder pathology using other radiological techniques. In addition, the pathology results from the subjects were primary gallbladder tumors except in the patient with porcelain gallbladder. Adenomatosis or polyposis-added secondary malignancy could have caused different diffusion findings (19). There was diffuse-solid wall thickening in all subjects. Primary solid components can be cleared off by widening necrotic areas in degenerate tumors, and necrotic components have a similar diffusion view with that of inflammation (20).

In conclusion, hyperintensity on DWI sequences was strongly correlated with malignant lesions. Therefore, according to the preliminary study presented here, DWI was a significantly sufficient examination technique in terms of showing whether qualitative or quantitative evaluation can be used to distinguish diffuse bladder malignancy from cholecystitis.

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