Abbreviated Title Page

Apparent diffusion coefficient as a potential surrogate marker for Ki-67 index in mucinous breast carcinoma

Abstract

Purpose

To examine the association between apparent diffusion coefficient (ADC), cellularity and Ki-67 index in mucinous breast carcinoma (MBC) compared with invasive carcinoma of no special type (NST). ADC's ability to identify lesions with highly-proliferating MBC was also examined.

Materials and Methods

Pathologically confirmed MBCs (mucinous group, n=18) and NSTs (control group, n=18) were retrospectively analyzed. ADC was calculated from signal intensity of diffusion weighted imaging at b values of 0 and 1000sec/mm^2. Ki-67 index and cellularity were histopathologically evaluated. The mucinous group was classified into high Ki-67 mucinous group (Ki-67 index ≥ 14%, highly-proliferating) and low Ki-67 mucinous group.

Results

In the mucinous group, minimum ADC (ADCmin) showed inverse correlation with cellularity (r=-0.802, p=<0.0001) and Ki-67 index (r=-0.825, p=<0.0001). In the control group, ADCmin showed inverse correlation with cellularity (r=-0.537 p=0.022), but no correlation with Ki-67 index (r=0.035, p=0.892). ADCmin of high Ki-67 mucinous group was significantly lower than that of low Ki-67 mucinous group (p=0.005).

Conclusion

This study demonstrated an inverse correlation between ADC and Ki-67 index in MBC and the ability of ADC to identify highly-proliferating MBC. Considering that ADC can evaluate whole lesions noninvasively, ADC may be a promising non-invasive surrogate marker for Ki-67 index in the risk stratification of MBC.

Key words:

ADC, Mucinous carcinoma, Breast cancer, Cellularity, Ki-67 index

INTRODUCTION

Diffusion weighted MR imaging (DWI) is well recognized as a useful non-contrast MR sequence for breast carcinoma(1). In various organs, including the breast, an inverse correlation between tumor cellularity and apparent diffusion coefficient (ADC; a quantitative parameter in DWI) is generally observed (2,3). Several DWI studies have demonstrated significantly lower ADC for breast carcinomas than for benign breast lesions (2-4).

In the clinical practice of breast cancer management, risk stratification is as important as distinguishing between malignant and benign. Since uncontrolled proliferation is a key feature of the progression of malignancy, immunohistochemical assessment of the nuclear antigen Ki-67 is now widely used as a tool for breast cancer stratification (5,6). The nuclear antigen Ki-67 is detectable in cells at all phases of the cell cycle except the G0 phase (7), and the Ki-67 index (the percentage of cells with Ki-67 positive nuclear immunostaining) is a measure of tumor proliferation. There is growing interest in the use of Ki-67 index as a pharmacodynamic biomarker of treatment efficacy in samples taken before, during, and after neoadjuvant therapy, particularly neoadjuvant endocrine therapy (6).

In previous reports (8,9), neither invasive carcinomas (various types) nor invasive ductal carcinomas of not otherwise specified type (equivalent to “invasive carcinoma of no special type” in the newest WHO classification (10)) showed significant correlation between ADC and Ki-67 index. Considering the inverse correlation between ADC and tumor cellularity (2,3), these results may imply that there is no correlation between cellularity and Ki-67 index in invasive carcinoma of no special type (NST).

In breast MR imaging, mucinous breast carcinoma (MBC) is dealt with differently from

other types of breast carcinoma, because MBC presents higher ADC than benign breast lesions and other malignant breast tumors due to abundant mucin and low cellularity, as reported by Woodhams et al.(11). Better prognostic factors have been reported in pure MBC than in mixed MBC(12,13), and in hypocellular type pure MBC than in cellular type (14), which suggested an association between cellularity and prognostic factors in MBC. Considering these special features of MBC, we hypothesized that ADC is associated with Ki-67 index in MBC.

The aims of this study were 1) to examine the association between ADC, cellularity and Ki-67 index in MBC compared to luminal-type NST, and 2) to evaluate the potential of ADC to distinguish between highly proliferating and low proliferating MBC.

MATERIALS AND METHODS

Patients

Approval for this study was obtained from the Institutional Review Board of our institution, and informed consent was waived due to retrospective study design. Between September 2008 and March 2012, 17 females (mean age=58.6 years, age range=39-76 years) were pathologically diagnosed with mucinous breast carcinoma (hypocellular type of pure MBC, 11; cellular type of pure MBC, 5; mixed MBC, 1) at our institution. As a control group, 17 female patients (mean age=60.5 years, age range=43-80 years) diagnosed with luminal-type NST during the same period of time were selected, matched for histological grade, MR scan date (within two months) and MR scanner type (3.0 T/ 1.5 T). Every patient underwent breast MRI scan and pathological evaluation by core needle biopsy (CNB) or surgery at intervals of two months maximum. Patients receiving neoadjuvant endocrine therapy (NAE) or neoadjuvant chemotherapy (NAC) underwent

MRI scans and pathological evaluations at the same period of therapies (pre- / post-).

Seventeen patients with MBC (14 without neoadjuvant therapy, 2 post NAE, 1 pre & post NAE) provided 18 lesions (mucinous group: hypocellular type of pure MBC, 11; cellular type of pure MBC, 5; mixed MBC, 2). Seventeen patients with luminal-type NST (14 without neoadjuvant therapy, 2 post NAC, 1pre & post NAC) provided 18 lesions (control group).

MRI Acquisition

Between September 2008 and March 2012, breast MRI was performed with a 3.0/1.5 T scanner (MAGNETOM Trio/Avant, A Tim System, Siemens AG) with 16/4ch breast coil. Routinely, T2-weighted, T1-weighted, Diffusion-weighted and fat-suppressed T1-weighted dynamic contrast enhancing images were obtained. Bilateral breast diffusion-weighted images were obtained using the following parameters: axial orientation, single shot-EPI, TR/TE 7000/62 ms, FOV 330×160 mm, matrix 166×80, thickness 3 mm, NEX 3, 48 slices. Other parameters were as follows: T2-weighted images; 6000/85-87ms, thickness 2.5mm / T1-weighted images; 3D-Gradient echo 4.87/2.45, thickness 1.25mm / fat-suppressed T1-weighted dynamic contrast enhancing images; pre- and post- (three times at 0–1, 1–2 and 5–6 min after gadolinium injection) contrast whole breast axial scanning in high temporal resolution for 1 min (3D-VIBE: R/TE 3.8/1.48 ms, FA 15 and FOV 330 mm×330 mm, matrix 448×461, 2.5 mm thickness, 60 slices), post contrast (at 2–5 min after gadolinium injection) whole breast coronal scanning in high-resolution (3D-VIBE: TR/TE 4.2/1.5 ms, FA 15, FOV 330 mm×330 mm, matrix 448×412, thickness 0.8 mm, 176 slices). Infused gadolinium contrast materials were either Gadoteridol (ProHance, Eisai Inc., Tokyo, Japan) or Gadodiamide

(Omniscan, Daiichi-Sankyo Inc., Tokyo, Japan) at a dose of 0.2 ml/kg power injected at a speed of 2.0 ml/s and flushed with 20 ml of saline at the same rate.

Image Analysis

Breast carcinoma lesions were detected and analyzed by diffusion-weighted images in association with T2-weighted, T1-weighted and dynamic contrast enhancing images in order to accurately identify the lesions.

ADC values were calculated using the algorithm presented by the following equation: $ADC=[1/(b_2-b_1)]\times In\ [S_1/S_2]$, where S_1 and S_2 are the signal intensities in the region of interest (ROI) obtained by two gradient factors, b_1 and b_2 (b_1= 0 sec/mm^2, b_2=1000 sec/mm^2). Inside the breast carcinoma lesions, placing as many 3×3 mm circle ROIs as possible without overlapping areas, the average ADC (ADCave) and the minimum ADC (ADCmin) values were obtained. At this time, cystic or necrotic areas were carefully excluded by checking T2-&T1-weighted and dynamic contrast enhancing images. These radiological evaluations were made by a breast radiologist (SK; 15 years of experience).

Pathological Analysis

Specimens were resected surgically and fixed overnight in 10% neutralized buffered formalin, then cut into 5 mm slices, and embedded in paraffin. Paraffin-embedded samples were serially sliced into 4 μm slices, and deparaffined by xylene. Serial sections were stained with hematoxylin-eosin (HE), and immunostained using anti-estrogen receptor (ER) antibody and anti-Ki-67 antibody (DAKO Cytomation, Glostrup, Denmark). Pathological diagnoses were made by breast pathologists (TRK with 13 years of experience and YM with 24 years of experience) independently.

The average of the estrogen receptor (ER) positivity was 95.7% (range 70-100%) in the mucinous group and 98.3% (range 90-100%) in the control group.

Ki-67 Index

The Ki-67 index was assessed microscopically. All tumor cell nuclei with homogenous granular staining, multiple speckled staining, or nucleolar staining were considered positively stained regardless of intensity, while any cytoplasmic immunoreactivity was considered non-specific, and hence not taken into consideration. Scoring was performed in the areas with highest number of positive nuclei (hot spot) within the tumor. The Ki-67 index was expressed as the percentage of Ki-67 positive malignant cells in 1,000 malignant cells assessed under high power magnification (×400).

In the context of the St. Gallen consensus 2013 (15), we classified the mucinous group into “low Ki-67 mucinous group (Ki-67 index; <14%)” and “high Ki-67 mucinous group (Ki-67 index; ≥14%)”.

Analysis of Tumor Cellularity

Pathologists initially selected the areas with highest number of Ki-67 positive nuclei (hot spot), its adjacent area, and lowest number of Ki-67 positive nuclei (cold spot) in each specimen stained by Ki-67. At 20-fold magnification, these three fields of view (FOVs: 1.6×1.2mm) were digitally photographed and saved as image files. HE- and ER-stained slides were likewise photographed at the same FOVs. In this way, 9 image files were saved for each specimen. From these image files, the tumor cellularity was analyzed according to the methods of previous studies (2,11).

All ER-stained images were converted to RGB color mode. In each image, some ER

positive tumor cell nuclei were selected using the range selection tool, and their RGB thresholds were computed. Adjusting the RGB thresholds of each image according to the computed values, only ER-positive tumor cell nuclei were visualized. Each ER stained image was converted to black & white mode and the binarized image was obtained. Using histogram, composition area ratio of ER positive tumor cell nuclei (=[counts of black pixels / total pixels]×100) was calculated. Multiplying this ratio by 100/ER positivity, tumor cellularity was calculated. Three values were calculated for each specimen from three FOVs. Considering the correspondence to Ki-67 index, the maximum value among the three was chosen as the tumor cellularity.

Statistical Analysis

Statistical analysis was performed with JMP10 (SAS institute). Correlation between ADCmin/ave, tumor cellularity and Ki-67 index was evaluated using Pearson's correlation coefficient. ADC values of the high Ki-67 mucinous group and low Ki-67 mucinous group were compared using Mann-Whitney test. A P value of less than 0.05 was considered statistically significant.

RESULTS

Correlation between ADCmin/ave, tumor cellularity and Ki-67 index is summarized in Table 1. In the mucinous group, ADCmin showed an inverse correlation with cellularity ($r=-0.802$, $p<0.0001$) (Figure1a) and with Ki-67 index ($r=-0.825$, $p<0.0001$) (Figure1b). Correlation between cellularity and Ki-67 index was also significant ($r=0.633$, $p=0.005$). In the control group, ADCmin showed an inverse correlation with cellularity ($r=-0.537$, $p=0.022$), but no significant correlation with Ki-67 index($r=0.035$, $p=0.892$). There was

no significant correlation between cellularity and Ki-67 (r=0.032, p=0.899) in this group. ADCave showed correlation patterns similar to ADCmin in both the mucinous and control group, but correlations tended to be weaker with ADCave than with ADCmin (Table1).

When comparing the high and low Ki-67 mucinous groups, ADCmin of the high Ki-67 mucinous group was significantly lower than that of the low Ki-67 mucinous group (p=0.005) (Figure2a). The high Ki-67 mucinous group can be identified with a sensitivity of 100% and a specificity of 93% by using the cut-off value of ADCmin=1.27 $\times 10^{-3} mm^2$ /sec.

Among three different types of MBC, the mixed MBC and the cellular type of pure MBC showed lower ADCmin than the hypocellular type of pure MBC (Figure2b).

Microphotographs of specimens (HE staining and Ki-67 immunohistochemical staining) from two representative MBC lesions, and the corresponding MR images (ADCmap), are shown in Figure3 and 4. The hypocellular type of pure MBC lesion shows low cellularity, low Ki-67 index and high ADCmin (Figure 3), while the mixed MBC lesion shows high cellularity, high Ki-67 index and low ADCmin (Figure 4).

DISCUSSION

We demonstrate an inverse correlation between ADC and Ki-67 index in MBC. The high Ki-67 mucinous group presented significantly lower ADCmin than the low Ki-67 mucinous group and can be classified with the cut-off value of ADCmin=1.27 $\times 10^{-3} mm^2$/sec. These results suggest the potential of ADC as a non-invasive surrogate biomarker for Ki-67 index. It should be emphasized that ADC can be used to evaluate the whole lesion non-invasively, while Ki-67 index only evaluates a limited part of the lesion

sampled by biopsy.

MBC is generally known for its relatively favorable prognosis, but MBC contains subtypes with aggressive progression and prognosis (16). Therefore, evaluating the cellular proliferative potential is crucial in the appropriate treatment of MBC. Ki-67 index is currently of interest as a pharmacodynamic biomarker of treatment efficacy in samples taken before, during, and after neoadjuvant therapy, particularly neoadjuvant endocrine therapy. Our results suggest that ADC can be used for this purpose in MBC.

In the control group, ADCmin showed an inverse correlation with cellularity, but no significant correlation with Ki-67 index. This is different from the results in the mucinous group, where ADCmin and cellularity showed significant correlation with Ki-67 index. These contrasting results may be explained by considering the relation between cellularity and Ki-67 index from a histopathological viewpoint. NST morphologically vary considerably and may contain extremely variable stromal components (e.g. foci of elastosis, focal necrosis) (10). As cellularity is affected by the ratio between the area for the tumor cells and the surrounding stroma, it is speculated that cellularity is affected by the presence of stromal components such as central necrosis or fibrosis (CNF). Considering that high Ki-67 index is associated with CNF in invasive ductal breast carcinoma (17) and lymph node-negative breast cancer (18), breast cancer with high Ki-67 index may not necessarily have high cellularity, which is compatible with the result in the control group where no correlation was seen between cellularity and Ki-67 index. In contrast, the correlation between cellularity and Ki-67 index seen in the mucinous group may imply that MBC, characterized by proliferation of nests of cells floating in lakes of mucin (16), has less stromal components that affect cellularity.

The association between subtypes, cellularity and prognostic factors in MBC has been

previously described. MBC can be classified into 3 subtypes: hypocellular type of pure MBC (major type), cellular type of pure MBC, and mixed MBC (containing non-mucinous “cellular” components consisting of infiltrating carcinoma without extracellular mucin). Anan et al(13) reported that incidences of lymphatic vessel invasion and nodal involvement were lower in pure MBC than in mixed MBC. Fentiman et al(12) reported that pure MBC had significantly better relapse-free and overall survival than mixed MBC. These reports suggest the importance of differentiating mixed MBC from pure MBC. Also, differentiation of the cellular type of pure MBC from the hypocellular type may be important according to Clayton(14), who demonstrated good correlation between low cellularity and survival in pure MBC. In our study, the mixed MBC and cellular type of pure MBC presented significantly lower ADCmin than the hypocellular type of pure MBC. MBC has been excluded from several reported studies in the potential use of ADC for breast cancer detection because of its high ADC mimicking benign lesions (11,19). Our results suggest ADC may have the ability for detecting MBC with the poorer prognosis. If we can obtain the same result on larger sample size in the future, it might be helpful for the detection and risk stratification of MBC.

The above discussion further indicates a wider application of ADC as a biomarker of cell proliferation in additional situations. ADC is particularly associated with Ki-67 index in MBC because cellularity is associated with tumor aggressiveness (12-14). If we can identify the specific situations where cellularity is associated with cell proliferation (e.g. among specific subtype or during chemotherapy), ADC may be used as a biomarker of cell proliferation in such situations, not limited to MBC.

Another interesting result from the current study is that ADCmin is a better surrogate marker than ADCave for Ki-67 index in MBC. Although ADCmin and ADCave showed

an inverse correlation with Ki-67 index in the mucinous group, ADCmin showed a stronger correlation with Ki-67 index than ADCave. Considering that Ki-67 index is calculated using the “hot spot” counts in the pathology specimen, it is reasonable that ADCmin, reflecting information from presumably the most “cellular” area, is a better marker for Ki-67 index than ADCave.

A few limitations of this study should be noted. Firstly, luminal-type NST lesions (average ER positivity 98.3%) were selected as a control group because all lesions in the mucinous group were luminal-type (average ER positivity 95.7%), and cellularity was evaluated using ER stained images. Therefore, these study results cannot be applied to HER2 type and triple negative type. Retrospective study design and small sample size are other limitations, though these were inevitable because of the low frequency of MBC.

In conclusion, our analysis demonstrated 1) the inverse correlation between ADC and Ki-67 index in MBC, and 2) the ability of ADC to classify highly proliferating MBC from those that are low proliferating. Considering the advantage of ADC in evaluating whole the lesion non-invasively, in contrast to Ki-67 index which only evaluates part of the lesion, ADC may be a promising non-invasive surrogate marker for Ki-67 index in the risk stratification of MBC.

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Table1

Correlation between ADCmin/ave, cellularity and Ki-67 index in mucinous group and control group; ADCave shows correlation patterns similar to ADCmin, but with larger p-values and weaker correlation than ADCmin

	ADCmin		ADCave	
	r	P-value	r	P-value
Mucinous group				
ADC vs. Cellularity	-0.802	<0.0001	-0.788	0.0001
ADC vs. Ki-67 index	-0.825	<0.0001	-0.695	0.001
Cellularity vs. Ki-67 index	0.633	0.005	0.633	0.005
Control group				
ADC vs. Cellularity	-0.537	0.022	-0.412	0.090
ADC vs. Ki-67 index	0.035	0.892	0.005	0.985
Cellularity vs. Ki-67 index	0.032	0.899	0.032	0.899

ADC; apparent diffusion coefficient

ADCmin; the minimum ADC

ADCave; the average ADC

r; Pearson’s correlation coefficient

Figure Legends

Figure1

Correlations between ADCmin, cellularity and Ki-67 index in mucinous group

a). An inverse correlation is indicated between ADCmin and cellularity (r=-0.802, $p<0.0001$).

b). An inverse correlation is indicated between ADCmin and Ki-67 index (r=-0.825, $p<0.0001$).

Figure2

Distribution of ADCmin in mucinous group

a). High Ki-67 mucinous group (Ki-67 index; ≥14%) shows significantly lower ADCmin than low Ki-67 mucinous group (p=0.005; Mann-Whitney test).

b). Mixed MBC and cellular type of pure MBC show lower ADCmin than hypocellular type of pure MBC.

Figure3

Representative case of pure MBC (hypocellular type)

a). HE-stained specimen (×40); shows clusters of carcinoma cells floating in lakes of mucin, representing hypocellular nature.

b). Ki-67 immunohistochemical stained specimen (×40); shows nuclei of tumor cells positively stained (brown) (Ki-67 index=7.4%).

c). Corresponding MR image (ADC map); shows lobulated mass with high ADC (ADCmin=$1.90\times10^{-3}mm^2$ /sec).

Figure4

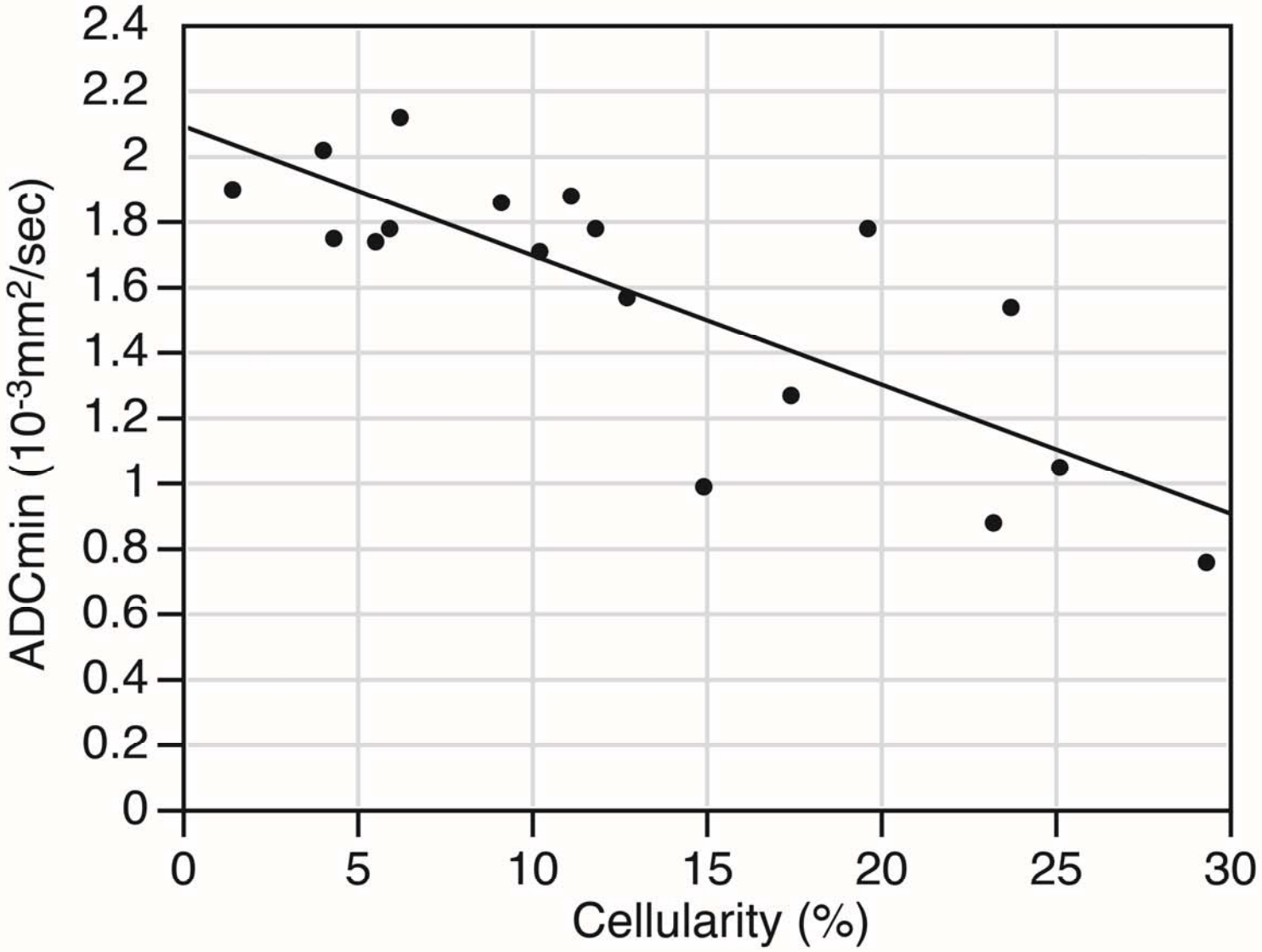
Representative case of mixed MBC

a). HE-stained specimen (×40); shows large clusters of cells along with mucus reflecting higher cellularity.

b). Ki-67 immunohistochemical-stained specimen (×40); shows relatively large number of positively-stained nuclei (brown) (Ki-67 index=34.7%).

c). Corresponding MR image (ADC map); shows round mass with low ADC (ADCmin=$0.88\times10^{-3}mm^2$ /sec).

a)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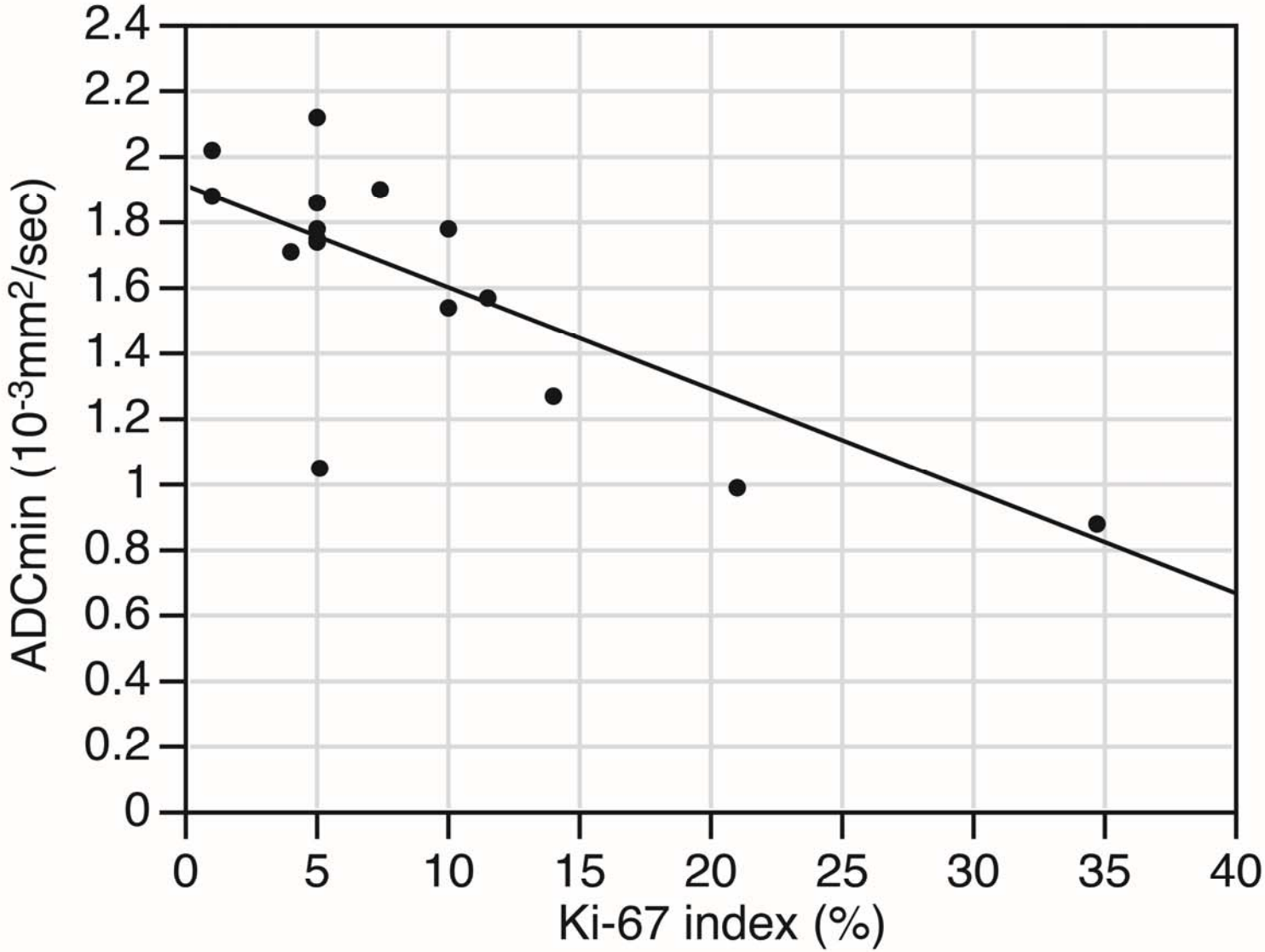
2.2
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
ADCmin (10-3mm2/sec)
0
5
10
15
20
25
30
Cellularity (%)

Figure 1

b)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2.2
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0.8
0.6
0.4
0.2
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ADCmin (10-3mm2/sec)
0
5
10
15
20
25
30
35
40
Ki-67 index (%)

Figure 1

a)

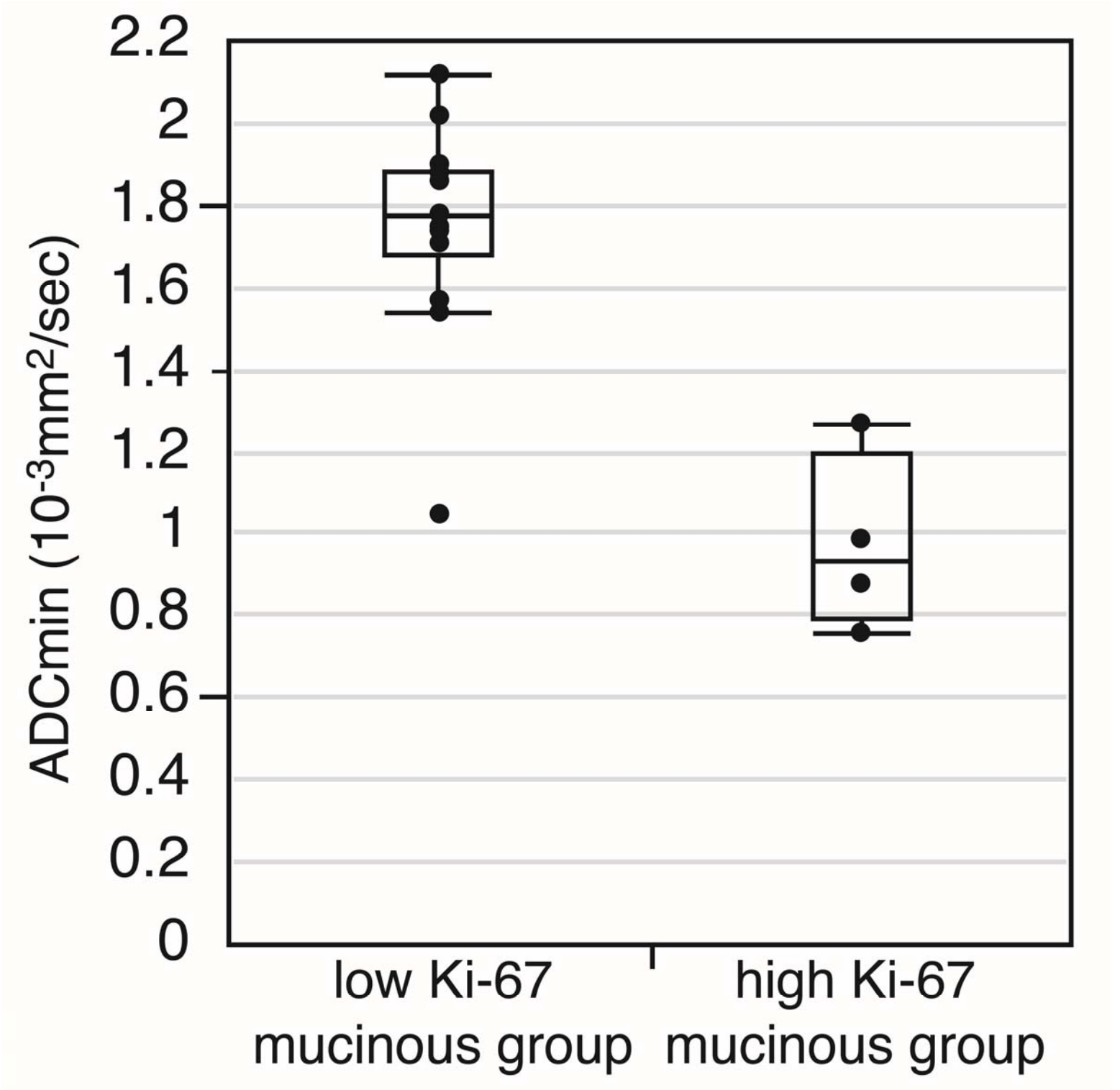
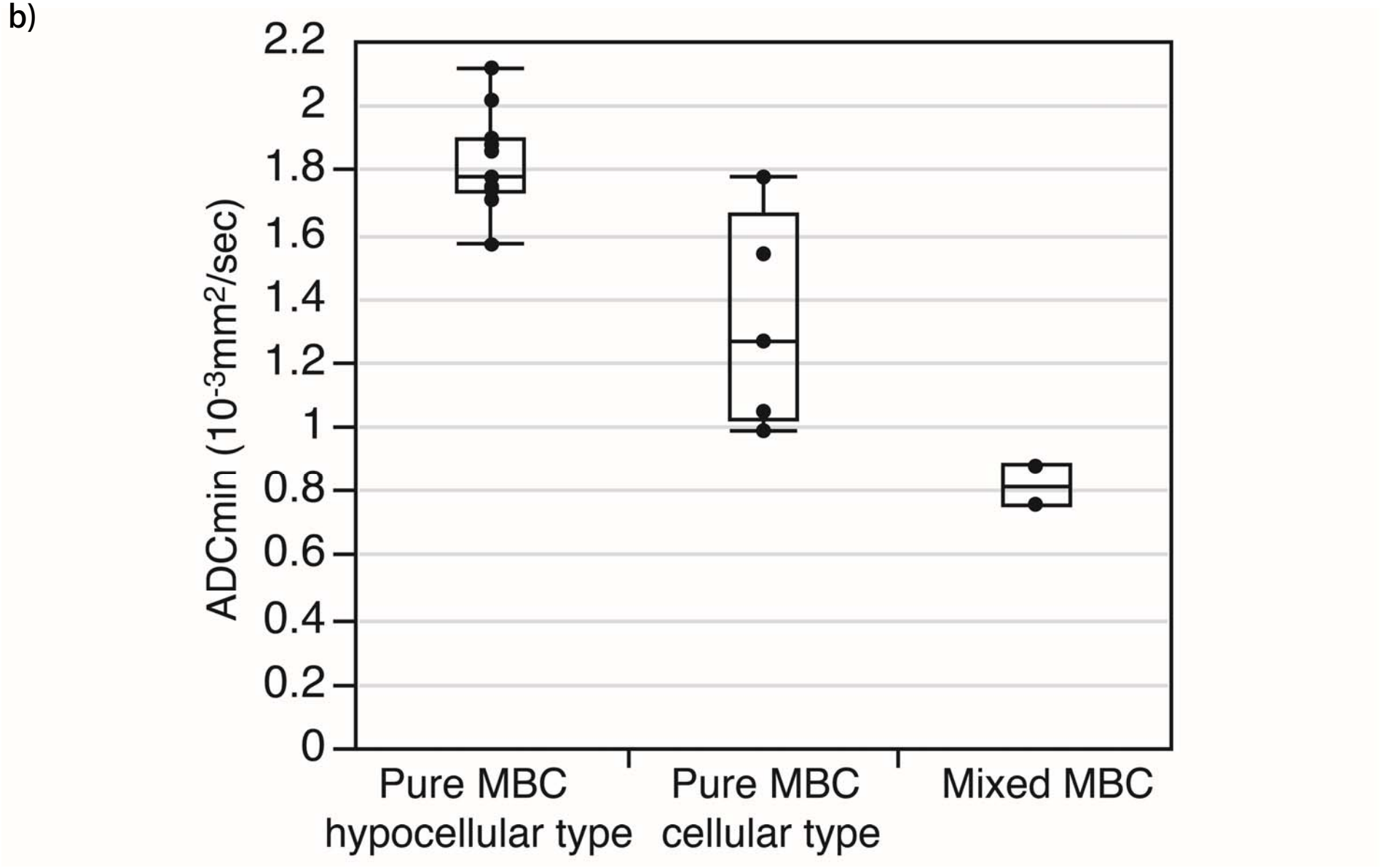

2.2
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
ADCmin (10-3mm2/sec)
low Ki-67
mucinous group
high Ki-67
mucinous group

Figure 2

b)


2.2
2
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1.2
1
0.8
0.6
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0.2
0
ADCmin (10-3mm2/sec)
Pure MBC hypocellular type
Pure MBC cellular type
Mixed MBC

Figure 2

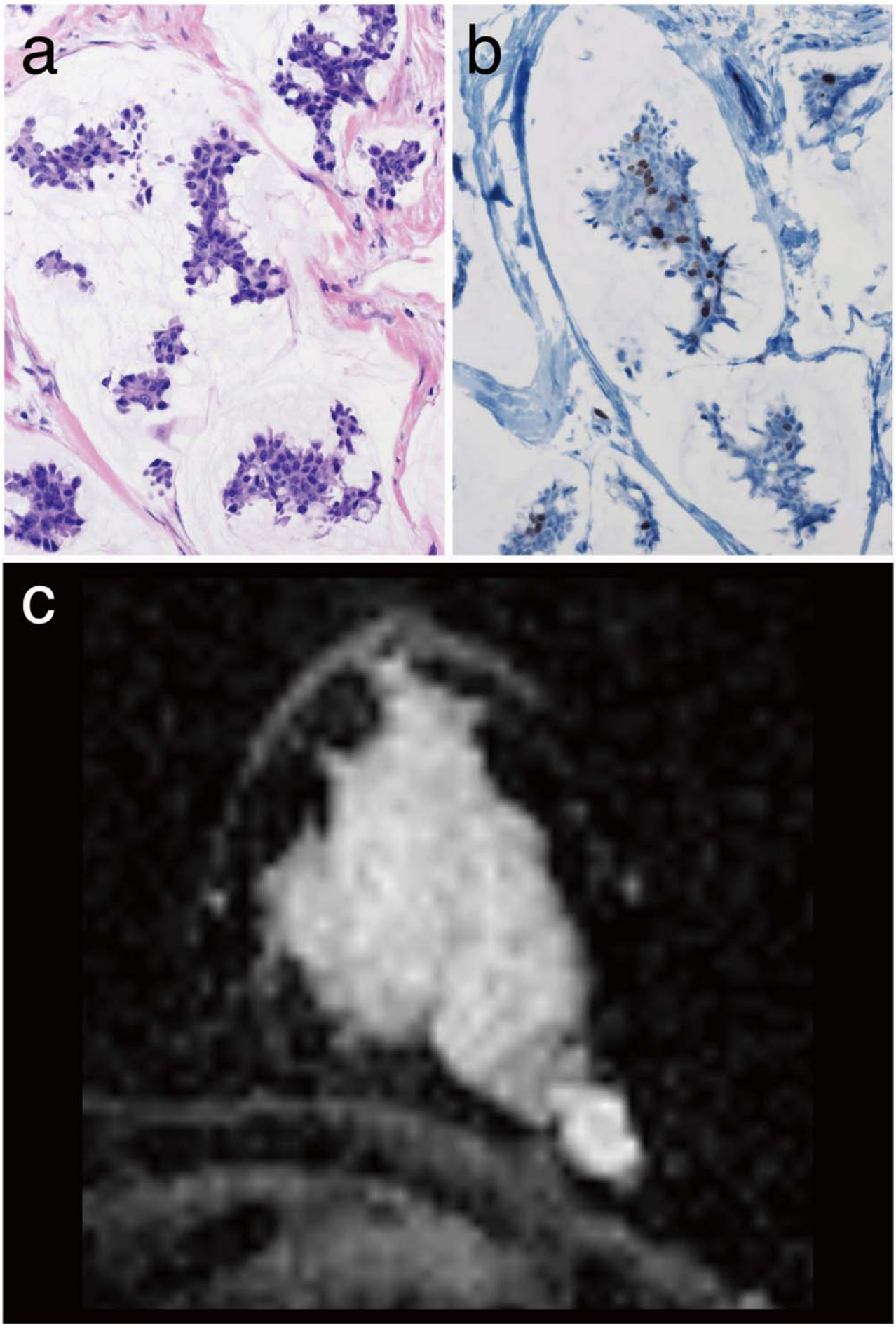

Figure 3

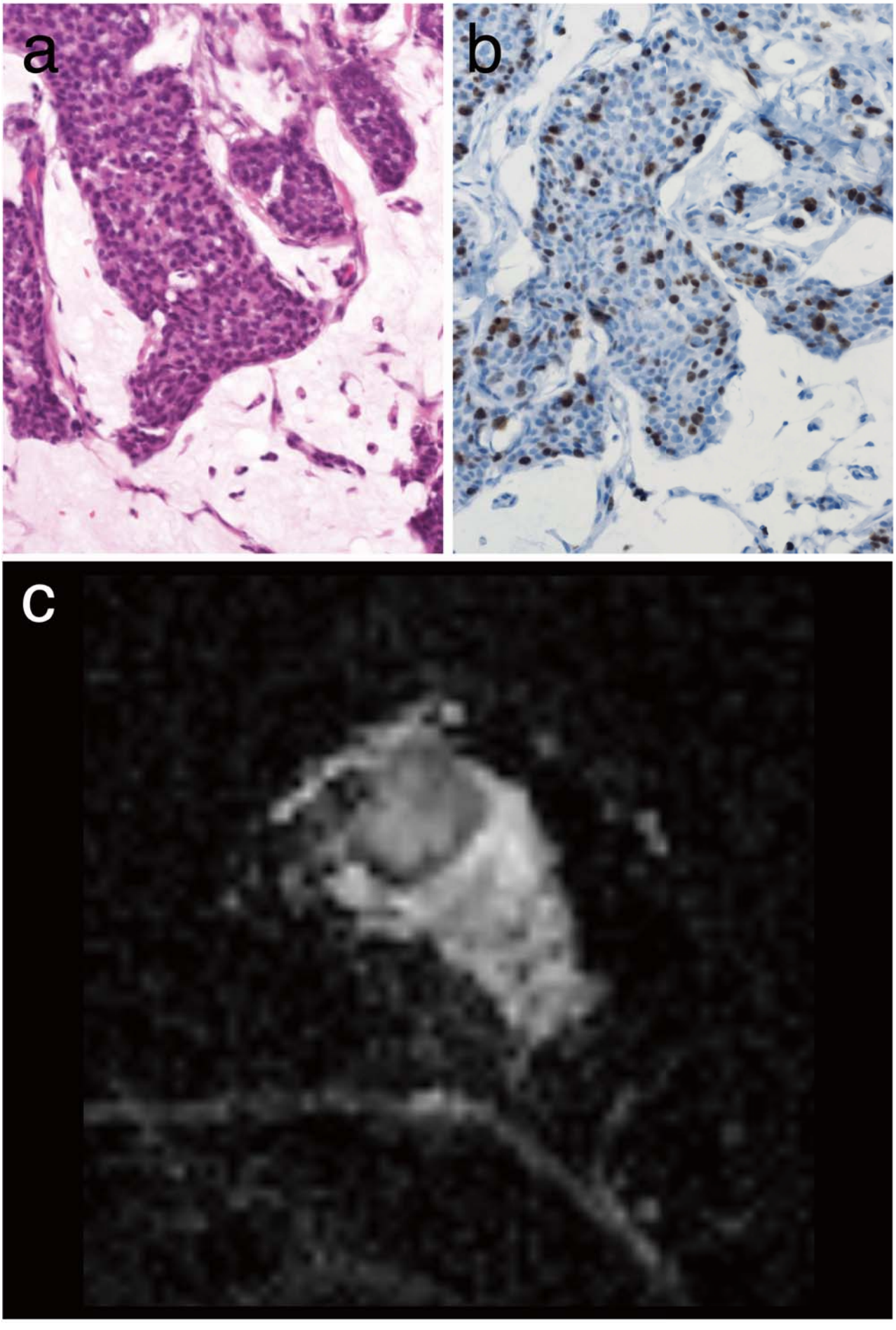

Figure 4