Title：

Predicting Metastasis in Clinically Negative Axillary Lymph Nodes with Minimum Apparent Diffusion Coefficient Value in Luminal A-like Breast Cancer

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Abstract

Background: We investigated the usefulness of the minimum ADC value of primary breast lesions for predicting axillary lymph node (LN) status in luminal A-like breast cancers with clinically negative nodes in comparison with the mean ADC.

Methods: Forty-four luminal A-like breast cancers without axillary LN metastasis at preoperative clinical evaluation, surgically resected with sentinel LN biopsy, were retrospectively studied. Mean and minimum ADC values of each lesion were measured and statistically compared between LN-positive (n = 12) and LN-negative (n = 32) groups. An ROC curve was drawn to determine the best cut-off value to differentiate LN status. Correlations between mean and minimum ADC values and the number of metastatic axillary LNs were investigated.

Results: Mean and minimum ADC values of breast lesions with positive LN were significantly lower than those with negative LN (mean: 839.9 ± 110.9 vs. 1022.2 ± 250.0 × 10^{-6} mm^2/s, p = 0.027, minimum: 696.7 ± 128.0 vs. 925.0 ± 257.6 × 10^{-6} mm^2/s, p = 0.004). The sensitivity and NPV using the best cut-off value from ROC using both mean and minimum ADC were 100%. AUC of the minimum ADC (0.784) was higher than that of the mean ADC (0.719). Statistically significant negative correlations were observed between both mean and minimum ADCs and number of positive LNs, with

stronger correlation to minimum ADC than mean ADC.

Conclusions: The minimum ADC value of primary breast lesions predicts axillary LN metastasis in luminal A-like breast cancer with clinically negative nodes, with high sensitivity and high NPV.

Keywords

Breast cancer, Axillary lymph node metastasis, Magnetic resonance imaging, Diffusion weighed imaging

Abbreviations

ADC: apparent diffusion coefficient

DWI: diffusion weighted imaging

ER: estrogen receptor

HER2: human epidermal growth factor receptor 2

LN: lymph node

MRI: magnetic resonance imaging

NPV: Negative predictive value

PgR: progesterone receptor

PPV: positive predictive value

ROC: receiver-operating-characteristic

Introduction

Breast cancer is group of heterogeneous diseases rather than a single disease [1], and is categorized into intrinsic subtypes defined by gene expression profiling [2]. Intrinsic subtypes of breast cancer are associated with distinct prognoses; for example, luminal A breast cancer, has much better prognosis than other subtypes [2, 3]. Immunohistochemical examination of the levels of estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER2), and Ki-67 expression, which reflects cellular proliferation, is often used clinically as an alternative to gene expression profiling to classify breast cancer subtypes [1]. Luminal-type breast cancer is defined by the presence of ER and/or PgR and the absence of HER2 [1]. Among them, luminal-type breast cancer with high ER and/or PgR and a low Ki-67 index is categorized as luminal A-like [1].

Axillary lymph node (LN) status is an important prognostic factor in breast cancer [4]. The number of LN metastases is an independent prognostic factor in luminal-type breast cancer [5]. Furthermore, LN status is considered as one of the strongest predictors for late distant recurrence, defined as a recurrence of more than 5 years after initial treatment, in luminal-type breast cancers with low proliferation [6]. Increasing tumor size, presence of lymphovascular invasion, poor histologic grade, and

age are clinicopathological factors associated with axillary LN metastasis [7-9]. Sentinel LN biopsy is a standard procedure for early-stage breast cancer patients with clinically negative axillary LNs [10]. Non-invasive preoperative prediction of LN status through procedures such as magnetic resonance imaging (MRI) would be a desirable for determining the optimal management of axilla in luminal A-like breast cancer patients.

Several studies have compared diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) values on MRI with various pathological findings and biomarkers of breast cancer [11-14]. Several reports showed that the ADC values of breast lesions in patients with positive axillary LN metastasis were significantly lower than those with negative axillary LN metastasis [14-16]. In these previous studies, the mean ADC values of the lesion were used in the evaluations [11-16], however, the usefulness of the minimum ADC value was recently recognized for differentiating between malignant and benign breast masses [17], detecting invasive components in ductal carcinoma in situ [18], and distinguishing breast cancer subtypes [19]. According to Hirano et al., sensitivity and specificity of the minimum ADC values were higher than those of the mean ADC values for the differentiation of benign and malignant breast lesions [17]. Therefore, we hypothesized that the minimum ADC value would be a better predictor of axillary LN metastasis than the mean ADC value.

The purpose of this study was to investigate usefulness of the minimum and mean ADC values of primary breast lesions for predicting axillary LN status in patients with luminal A-like breast cancer who exhibited clinically negative axillary LNs.

Materials and Methods

Patients

This retrospective study was approved by our institutional review board, and informed consent was waived. From February 2012 to June 2013, breast cancer patients who underwent breast MRI including DWI at 3-tesla before surgery were studied. Inclusion criteria were 1) no axillary LN metastasis observed on preoperative clinical comprehensive evaluation by physical examination, ultrasound, and computed tomography, 2) surgical resection of breast cancer with sentinel LN biopsy was performed, and 3) luminal A-like breast cancer was pathologically proven in the operation specimen. In this study, luminal A-like breast cancer was defined as high ER (greater than or equal to 70%), negative HER2 (0 or 1+ staining by immunohistochemistry, or 2+ staining without HER2-gene amplification confirmed by dual color *in situ* hybridization), and a Ki-67 index of less than 14%. The Ki-67 index was assessed as the percentage of tumor cells, out of >1000 invasive tumor cells, that showed definite nuclear staining by automated scoring. Exclusion criteria were 1) chemotherapy, or 2) hormonal therapy applied before the operation. After exclusion, 41 patients were enrolled in this study. The median age was 59 years old (range: 40 to 79), and all the patients were women. The median interval between MR examination and

surgery was 28 days (range: 7 to 91).

There were 44 luminal A-like breast cancers in 41 patients; three patients had bilateral luminal A-like cancers. Of the 44 lesions, there were 35 invasive ductal carcinomas, six invasive lobular carcinomas, one tubular carcinoma, one invasive micropapillary carcinoma, and one mucinous carcinoma.

Axillary LN dissection was added for eight lesions because sentinel LN was positive in pathological diagnosis during surgery. In the final pathological diagnosis after the operation, 12 of the 44 lesions had axillary LN metastasis; in four lesions, sentinel LN metastasis was revealed in the permanent specimen although sentinel LN was negative in pathological diagnosis during surgery. In this study, sentinel LNs obtained during surgical operation were sliced along the long axis, according to their thickness. Sentinel LNs were initially examined in intraoperative frozen sections stained with hematoxylin and eosin. All sentinel LNs were finally diagnosed using fixed sections with hematoxylin and eosin stain, as well as cytokeratin immunostaining. According to the 8th edition of the TNM Classification of Malignant Tumors from the Union for International Cancer Control (UICC) [20], macro- (>2 mm) and micrometastases (0.2–2.0 mm) were considered to be positive, and isolated tumor cell clusters (≤0.2 mm or <200 cells) were considered to be negative. A summary of the

pathological diagnoses of axillary LNs is shown in Figure 1.

Pathological factors of each lesion, such as size of tumor (the largest diameter of the invasive component on the pathological specimen), histological grade, lymphovascular invasion, expression of ER**,** and the Ki-67 index were obtained from the histopathological report.

MRI technique

MR imaging was performed with a 3-tesla system (Achieva TX, Phillips Medical Systems, Best, The Netherlands). A 7-channel breast coil was used, with the patients in prone position. DWI was acquired bilaterally in the axial plane with an echo planner image sequence with fat suppression: TR: 10,000 ms, TE: 52 ms, TI: 250 ms, FOV: 320 × 267 mm, voxel size: 3.33 × 4.18 × 5.00 mm, slice gap: 2 mm, NSA: 2, b-value: 0, 1000 s/mm^2, and SENSE factor: 2. Short inversion-time inversion recovery with slice selection gradient reversal was used for fat suppression. The ADC values were calculated from two DWI scans acquired with a b-factor of 0 and 1000 s/mm^2. The ADC maps were reconstructed by calculating the ADC values in each pixel of each section.

Of 44 lesions, 24 (54.5%) were examined by MRI before biopsy and 20

(45.5%) were examined after biopsy.

Image Analysis

The mean and minimum ADC values of each cancerous breast lesion were measured by a board-certified radiologist specializing in breast MR imaging with 13 years of experience who manually placed regions of interest (ROI) within the targeted lesion on the ADC maps. The radiologist was informed that the patients were diagnosed with invasive breast cancer but was blinded to the pathological diagnosis of axillary LN of the patient. The oval-shaped ROI was put inside the lesion as large as possible while avoiding cystic, necrotic, and hemorrhagic areas and obvious artifacts. The slice with the largest ROI was selected for each lesion. When the lesion had both invasive and non-invasive lesions on the pathological specimen, ROIs were placed on the suspected invasive lesion on MRI.

Statistical Analysis

Clinical and histopathological characteristics were compared between the axillary LN positive group and negative group using the Mann-Whitney U test for quantitative data, and Fisher's exact test for categorical data. Mean and minimum ADC

values were compared between the axillary LN positive group and negative group using the Mann-Whitney U test. A receiver operating characteristic (ROC) curve was drawn to determine the best cut-off value of positive axillary LN. The area under the curve (AUC) of ROC curves between mean and minimum ADC values was compared statistically. The correlations between mean and minimum ADC values and number of axillary LN metastases were investigated using Spearman's correlation coefficients. The MedCalc 14.12.0 statistical software package (MedCalc Software bvba, Mariakerke, Belgium) was used for statistical analysis. All quantitative data are presented as the mean ± standardized deviation. A p-value < 0.05 was considered significant.

Results

A summary of clinical and pathological characteristics comparing the axillary LN positive and negative groups is shown in Table 1. The age of the axillary LN positive group was younger (54.6 ± 9.1 years old) than that of the LN negative group (61.2 ± 9.6 years old), but the difference was not significant ($p = 0.059$). Tumor size of the LN positive lesions (21.2 ± 8.4 mm) was significantly larger than that for the LN negative lesions (12.8 ± 7.4 mm) ($p = 0.004$). Lymphovascular invasion was seen significantly more frequently in LN positive lesions (five of 12, 41.7%) than in LN negative lesions (two of 32, 6.3%) ($p = 0.011$). Grade 2 cancer was found in 50% of the LN positive group (six of 12), but only in 21.9% of the LN negative group; however, this difference was not significant ($p = 0.135$). There was no grade 3 cancer in this study. The Ki-67 index was significantly higher for LN positive lesions (9.6 ± 2.1%) than for LN negative lesions (6.2 ± 3.8%) ($p = 0.006$).

The mean ADC value of breast lesions was significantly lower in the axillary LN positive group than in the axillary LN negative group (839.9 ± 110.9 vs. 1022.2 ± 250.0 × 10^{-6} mm^2/s, $p = 0.027$, Figure 2a). The minimum ADC value of breast lesions was also significantly lower in the axillary LN positive group than in the axillary LN negative group (696.7 ± 128.0 vs. 925.0 ± 257.6 × 10^{-6} mm^2/s, $p = 0.004$, Figure 2b).

Representative cases of axillary LN positive and negative cancers are shown in Figures 3 and 4, respectively.

The ROC curve analysis showed that the best cut-off value of mean ADC for axillary LN positive was 972.9 × 10^{-6} mm^2/s with 100% sensitivity and 50% specificity (AUC = 0.719, p = 0.005, Figure 5). Using this cut-off, the positive predictive value (PPV) was 42.8% and the negative predictive value (NPV) was 100%. This analysis also showed that the best cut-off value of the minimum ADC for axillary LN positive was 852.2 × 10^{-6} mm^2/s with 100% sensitivity and 56.2% specificity (AUC = 0.784, p < 0.001, Figure 5). Using this cut-off, PPV was 46.1% and NPV was 100%. The AUC was higher for the minimum ADC value than for the mean ADC value, however the difference was not statistically significant (p = 0.188).

A weak, but statistically significant negative correlation was observed between the mean ADC value and the number of positive LNs (r_s = -0.364, p = 0.015, Figure 6a), and a moderate, statistically significant negative correlation was observed between the minimum ADC value and the number of positive LNs (r_s = -0.447, p = 0.002, Figure 6b).

Discussion

This study investigated the usefulness of the minimum ADC value of primary breast lesions for predicting axillary LN status in patients with luminal A-like breast cancer with clinically negative axillary LNs in comparison with the mean ADC value. In luminal A-like breast cancer patients with clinically negative axillary LNs, both the mean and minimum ADC values of primary breast lesions with positive axillary LN metastasis were significantly lower than those with negative axillary LN metastasis, and that the sensitivity and NPV, using the best cut-off value from ROC analysis using both of mean and minimum ADC values, were 100%. Further, the minimum ADC value appeared to better discriminate between LN positive and negative breast cancer than the mean ADC value, with a higher AUC value in ROC analysis and stronger correlation to the number of positive LNs.

Luminal breast cancer, especially luminal A breast cancer, has better prognosis than other subtypes [2, 3]. The axillary LN involvement; the number of axillary LN metastases, is an important prognostic factor in breast cancer [4]. According to Chen et al., LN involvement was an independent prognostic factor in luminal-type breast cancer [5]. We previously reported that LN status was one of the strongest predictors for late distant recurrence in luminal-type breast cancers with low proliferation [6]. Therefore, it

is desirable to evaluate LN status precisely before operating, using a non-invasive approach. Based on our results, prediction of LN status could be achieved with the mean and minimum ADC values in the primary lesion, especially for exclusion of LN metastasis, since sensitivity and NPV were 100% in luminal A-like breast cancer with clinically negative axillary LNs. Sentinel LN biopsy is considered a standard management for patients with early-stage breast cancer with clinically negative axillary LNs [10]. Recently, the concept that axillary LN dissection can be avoided in patients with one or two positive sentinel LNs when conventionally fractionated whole-breast radiation therapy is planned has been widely accepted [10]. By evaluating the mean and minimum ADC values of the primary breast cancer site, there is the potential to omit even sentinel LN biopsy in clinically LN negative luminal A-like breast cancer patients when the mean and minimum ADC value of primary breast lesion is high.

Several studies investigated the association of mean ADC values of the primary breast cancerous lesion with axillary LN status [12, 14-16]. Only one study reported there was no significant correlation between the mean ADC value and LN metastasis [12]. However, most of these studies showed the mean ADC value in patients with positive axillary LN metastasis was significantly lower than those with negative axillary LN metastasis [14-16]. In our study, the mean and minimum ADC values of primary

breast lesions with positive axillary LN metastasis was significantly lower than those with negative axillary LN metastasis. Our results were consistent with the majority of previous studies. According to Kim et al, when using a cut-off point of the mean ADC value of 991 × 10^{-6} mm^2/s for the primary breast tumor for predicting axillary LN metastasis, in early stage breast cancer patients, sensitivity was 86.2% and NPV was 93.3%, and in a subgroup of clinically negative axillary LNs, sensitivity was 88.2% and NPV was 96.5% [16]. A meta-analysis that evaluated the diagnostic performance of the ADC value of the axillary LN itself revealed that the mean ADC value was significantly lower for metastatic LNs than for non-metastatic LNs, and the sensitivity was 89% [21]. In our study, using the optimal cut-off value for each mean and minimum ADC, we were able to predict the presence of axillary LN metastasis with a sensitivity and NPV of 100%, which was higher than that observed for previous studies.

In our study, the AUC of the minimum ADC value was higher than that of the mean ADC value in ROC analyses, and the minimum ADC value had a stronger negative correlation with the number of positive LNs than that for the mean ADC value. Therefore, the minimum ADC value can be considered a better parameter than the mean ADC value to evaluate axillary LN status. The usefulness of the minimum ADC value in breast cancer diagnosis has been reported to include differentiating malignant from

benign masses [17], detecting invasive components [18], and distinguishing between subtypes [19]. In this study, we showed the usefulness of the minimum ADC value in the prediction of LN status in luminal A-like breast cancer. The definition of the minimum ADC value in our study was different from that in several previous studies in which the minimum ADC value was defined as the lowest mean ADC value among multiple small ROIs placed within the targeted lesion [17, 18]. In our study, the minimum ADC value was defined as the lowest value in the single ROI within the targeted lesion. However, the definition of our minimum ADC value is commonly used elsewhere [19, 22-24].

It has been reported that the mean ADC value had an inverse correlation to tumor cellularity [25, 26], and an inverse correlation to the Ki-67 index in breast cancer [19]. In fact, the reason why the primary breast lesions with positive axillary LNs had lower ADC values is unclear. However, in our study, the Ki-67 indexes of LN positive lesions were higher than those of LN negative lesions. A higher Ki-67 index, which might be related to higher cellularity, would be associated with a lower ADC value in LN positive lesions in our study. Recently, it has been reported that heterogeneity of the tumor microenvironment was associated with LN metastasis in breast cancer [27]. In our study, since the minimum ADC value had higher diagnostic performance in

evaluating axillary LN status than the mean ADC, the minimum ADC value might reflect the more malignant portion within breast cancerous lesions that exhibit tumor heterogeneity. However, we did not attempt to directly compare MR images with histopathological specimens in this study. Further studies are needed to validate our hypothesis.

Our protocol used 3-tesla MRI. For wider application of the findings of this study to other institutions, we must consider differences between 1.5-tesla and 3-tesla systems. In general, 3-tesla systems provide better signal-to-noise and contrast-to-noise ratios than 1.5-tesla systems. However, regarding ADC measurements, Matusuoka et al. demonstrated no significant difference in ADC values between 3-tesla and 1.5-tesla systems for the same breast cancers [28]. Therefore, our results could be applied to 1.5-tesla systems.

Regarding the order between MRI examination and biopsy, less than half of the cancers were examined by MRI after biopsy. According to Latifoltojar et al., the ADC values of prostate tissue at 1, 2, and 6 months post-biopsy were not significantly different from pre-biopsy values [29]. Furthermore, we avoided placement of ROIs in hemorrhagic areas. Therefore, we speculate that the biopsy period did not have a significant effect on ADC measurement.

Age, tumor size, lymphovascular invasion, and histologic grade are known to be clinicopathological factors associated with axillary lymph node metastasis [7-9]. In our study, tumor size of LN positive lesions was significantly larger than that of LN negative lesions, the presence of lymphovascular invasion was significantly related to LN metastasis, and the LN positive patients tended to be younger with LN positive lesions tending to be of higher grade. Our results are consistent with previous studies. Although Kim et al reported that there were no significant associations between Ki-67 index and axillary LN status [16], the Ki-67 index of LN positive lesions was significantly higher than that of LN negative lesions in our study. This discrepancy might be the result of a difference in study population; as we studied only luminal A-like cancers, while Kim et al. studied various subtypes [16].

There are several limitations to the present study. First, in terms of study design, the study was retrospective at a single institution, which carries all the inherent limitations of retrospective investigations. Our study was small in size, and did not yield a statistically significant difference between the minimum and mean ADC of AUC in ROC analysis. A larger sized study could show statistically significant differences between these values. Therefore, further prospective, multi-centric and large size studies are needed to validate our results. Second, for each tumor, we placed the ROI to

measure the mean and minimum ADC values on only one slice. Placement of ROIs on multiple slices might provide a more accurate measurement of these values. Nevertheless, our method is simple and time efficient to apply in daily clinical practice.

In conclusion, with a high sensitivity and NPV, the minimum ADC value of primary breast lesions can be a better predictor than the mean ADC value for axillary LN metastasis in luminal A-like breast cancer with clinically negative axillary LN metastases. Our results might provide an opportunity to omit sentinel LN biopsy in clinically LN negative luminal A-like breast cancer patients with higher minimum ADC values in the breast lesion.

Conflict of Interest

K. Kudo received research grants from Hitachi Ltd and Philips Medical systems, as well as lecture fees from Hitachi Ltd, GE Healthcare, Siemens Healthcare, and Toshiba Medical Systems. The other authors have no conflict of interest to declare.

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Figure Legends

Figure 1: Summary of axillary lymph node (LN) status.

In the final pathological diagnoses, 12 lesions had positive and 32 lesions had negative axillary LNs.

ITC: isolated tumor cell clusters, meta: metastasis

Figure 2: Comparison of mean (a) and minimum (b) apparent diffusion coefficient (ADC) values of primary breast lesions between the axillary lymph node (LN) positive group and negative group.

Mean and minimum ADC values in the axillary LN positive group were significantly lower than that in the axillary LN negative group.

Figure 3: A representative case of positive axillary lymph node metastasis.

(a) Axial dynamic contrast-enhanced fat-suppressed T1-weighed imaging 60 seconds after administration of gadolinium; (b) axial diffusion-weighted imaging (DWI) with a b-value of 1000 s/mm^2; (c) the apparent diffusion coefficient (ADC) map.

A 51-year-old woman with Luminal A-like breast cancer (invasive ductal carcinoma; estrogen receptor: positive; progesterone receptor: positive; human epidermal growth

factor receptor 2: negative; Ki-67: 9.3%). An oval-shaped enhanced mass is seen in the right breast (a: arrow). On DWI the mass shows high intensity (b: arrow). On the ADC map, the mass shows low intensity (c: arrow), and the mean and the minimum ADCs of this lesion were 788 and 703 × 10^{-6} mm^2/s, respectively. Metastasis was revealed in eight axillary lymph nodes in the operation specimen.

Figure 4: A representative case of negative axillary lymph node metastasis.

(a) Axial dynamic contrast-enhanced fat-suppressed T1-weighed imaging 60 seconds after administration of gadolinium; (b) axial diffusion-weighted imaging (DWI) with a b-value of 1000 s/mm^2; and (c) the apparent diffusion coefficient (ADC) map.

A 64-year-old woman with Luminal A-like breast cancer (invasive ductal carcinoma; estrogen receptor: positive; progesterone receptor: positive; human epidermal growth factor receptor 2: negative; Ki-67: 3.5%). An oval-shaped enhanced mass is seen in the left breast (a: arrow). On DWI the mass shows high intensity (b: arrow). On the ADC map the mass shows low intensity (c: arrow), and the mean and the minimum ADC of this lesion were 1089 and 1049 × 10^{-6} mm^2/, respectively. There was no metastasis in the sentinel lymph node.

Figure 5: A receiver operating characteristic (ROC) curve analysis of the mean and minimum apparent diffusion coefficient (ADC) values for discrimination between axillary lymph node (LN) positive and negative for metastasis.

AUC of the minimum ADC value (0.784) was higher than that of the mean ADC value (0.719), however, the difference was not significant ($p = 0.188$).

Figure 6: Correlation between mean (a) and minimum (b) apparent diffusion coefficient (ADC) values of primary breast lesions and number of axillary lymph nodes (LN) positive for metastasis.

A weak, but statistically significant negative correlation was observed between the mean ADC and the number of positive axillary LNs ($r_s = -0.364$, $p = 0.015$, a), and a moderate, statistically significant negative correlation was observed between the minimum ADC and the number of positive axillary LNs ($r_s = -0.447$, $p = 0.002$, b).

Acknowledgements

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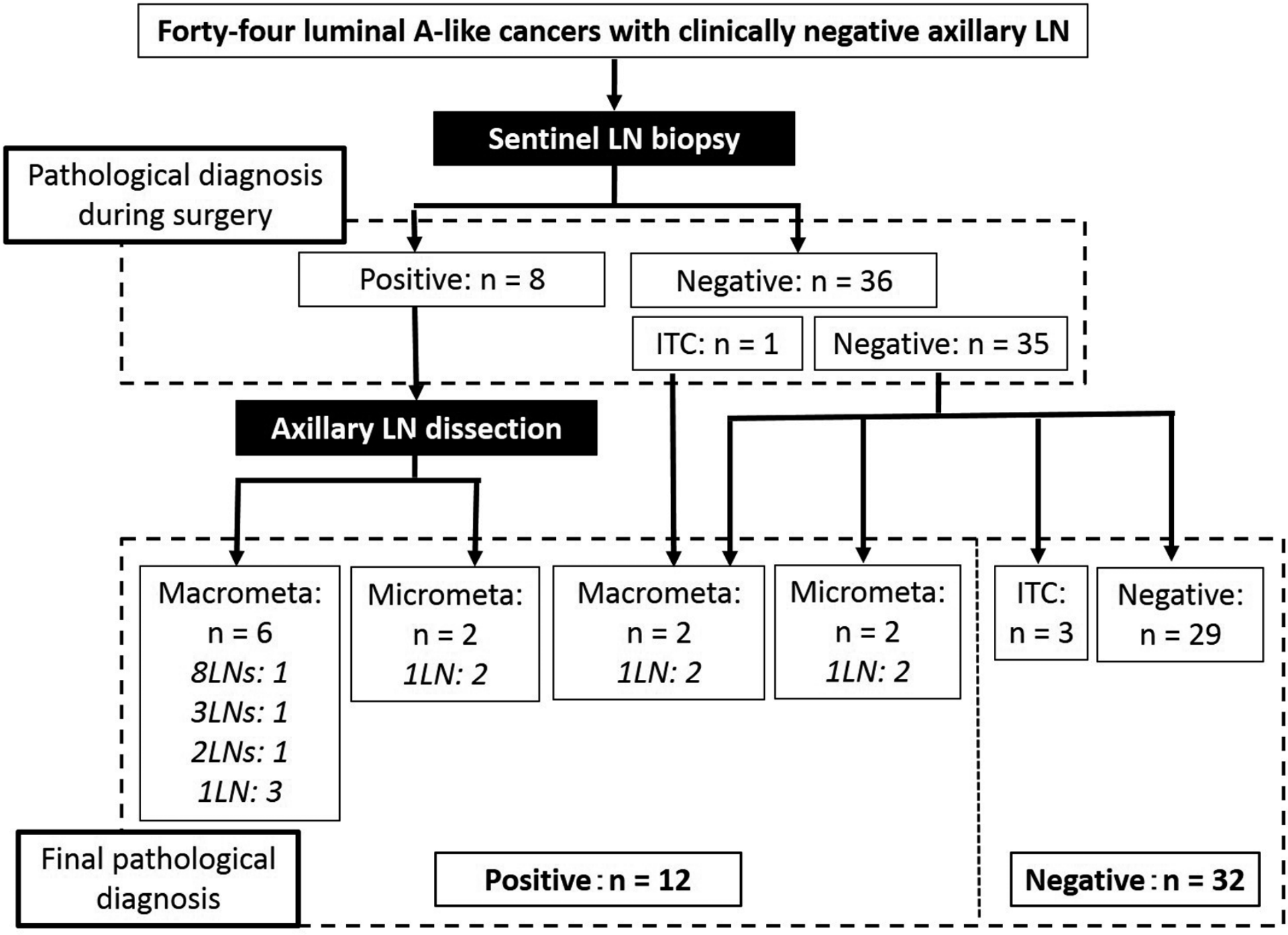
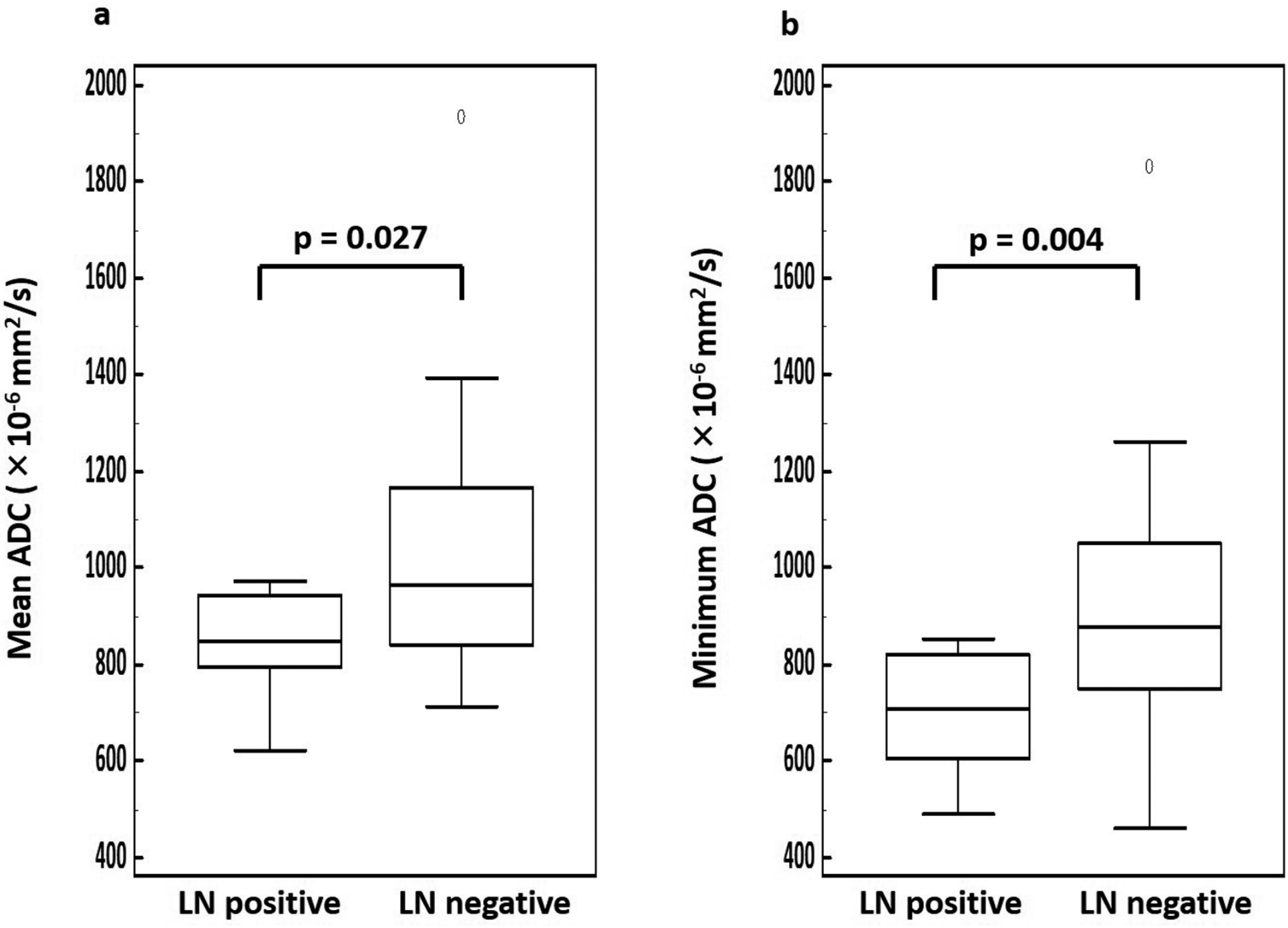
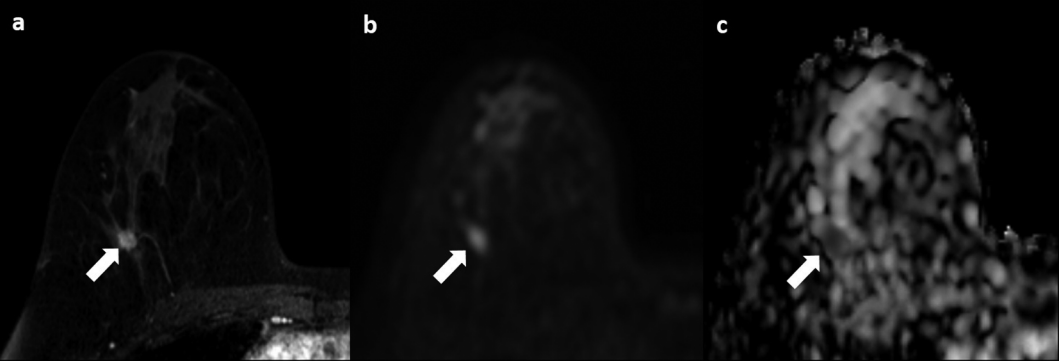
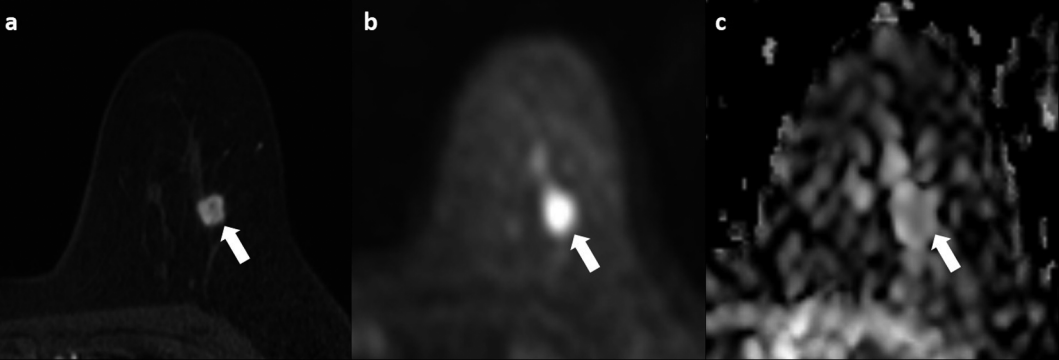
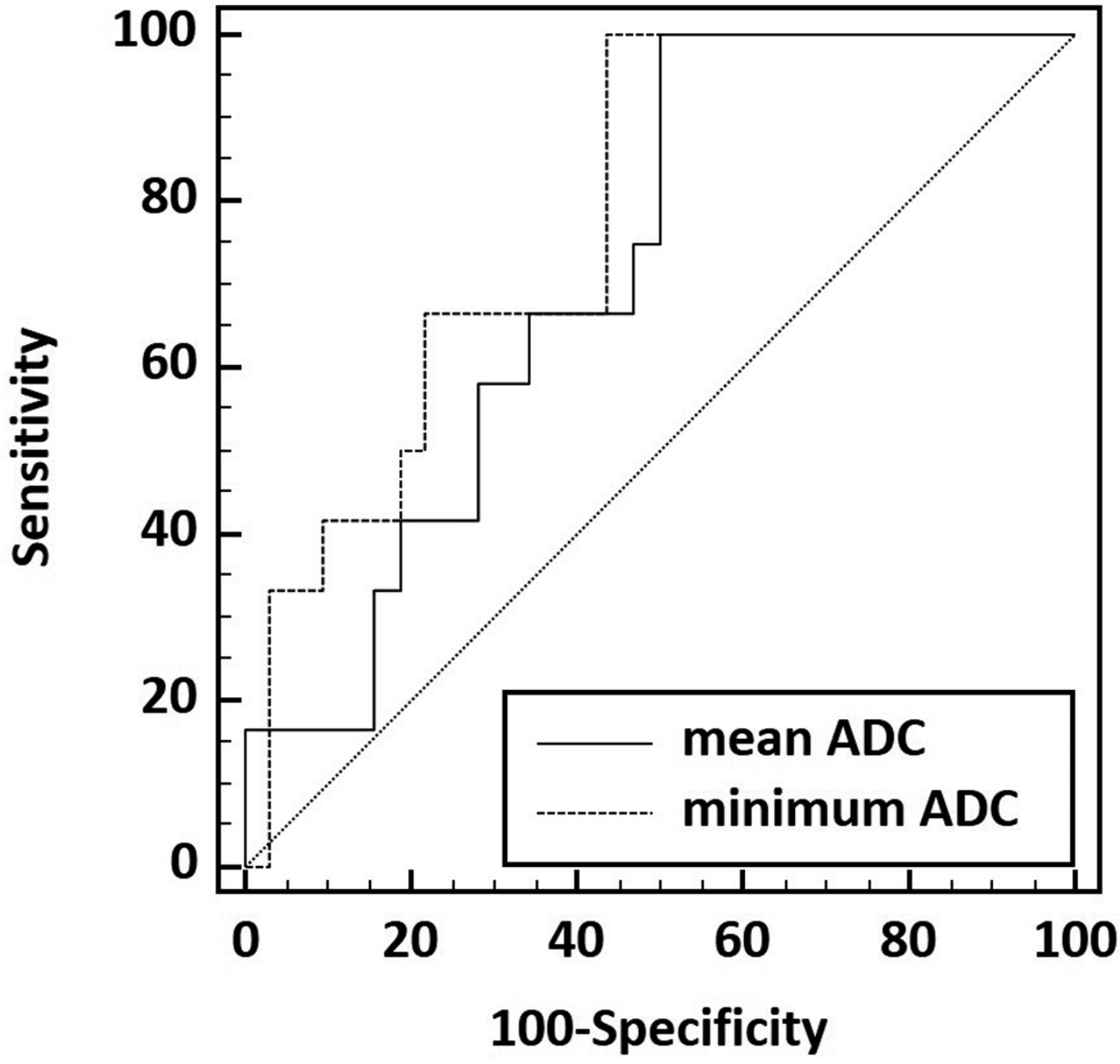
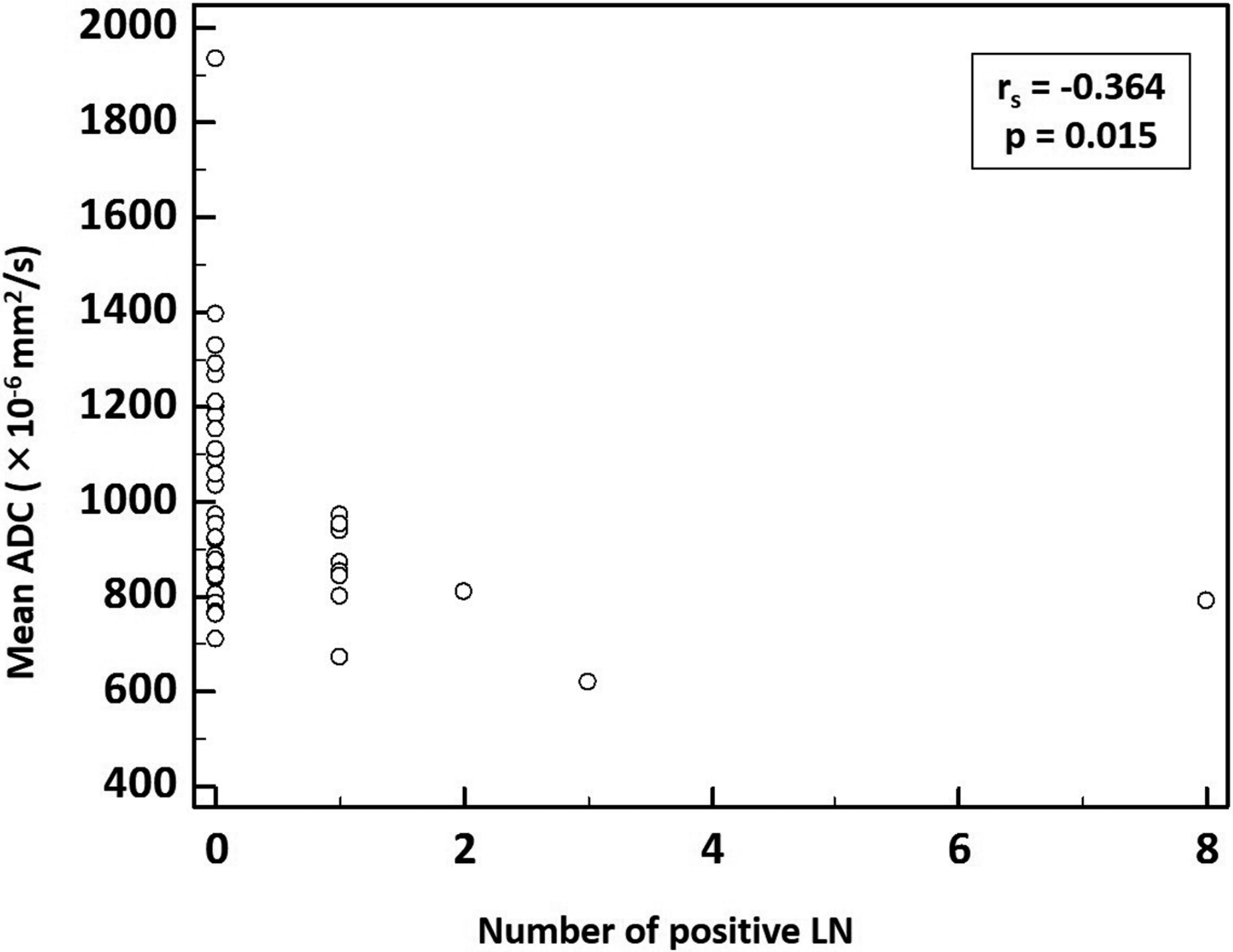

Forty-four luminal A-like cancers with clinically negative axillary LN
Sentinel LN biopsy
Pathological diagnosis during surgery
Positive: n = 8
Negative: n = 36
ITC: n = 1
Negative: n = 35
Axillary LN dissection
Macrometa: n = 6 8LNs: 1 3LNs: 1 2LNs: 1 1LN: 3
Micrometa: n = 2 1LN: 2
Macrometa: n = 2 1LN: 2
Micrometa: n = 2 1LN: 2
ITC: n = 3
Negative: n = 29
Final pathological diagnosis
Positive : n = 12
Negative : n = 32


a
2000
1800
1600
1400
1200
1000
800
600
400
Mean ADC (× 10-6 mm2/s)
p = 0.027
LN positive
LN negative
b
2000
1800
1600
1400
1200
1000
800
600
400
Minimum ADC (× 10-6 mm2/s)
p = 0.004
LN positive
LN negative


a
b
c


a
b
c


100
80
60
40
20
0
Sensitivity
0
20
40
60
80
100
100-Specificity
mean ADC
minimum ADC


2000
1800
1600
1400
1200
1000
800
600
400
Mean ADC (× 10-6 mm2/s)
0
2
4
6
8
Number of positive LN
rs = -0.364
p = 0.015

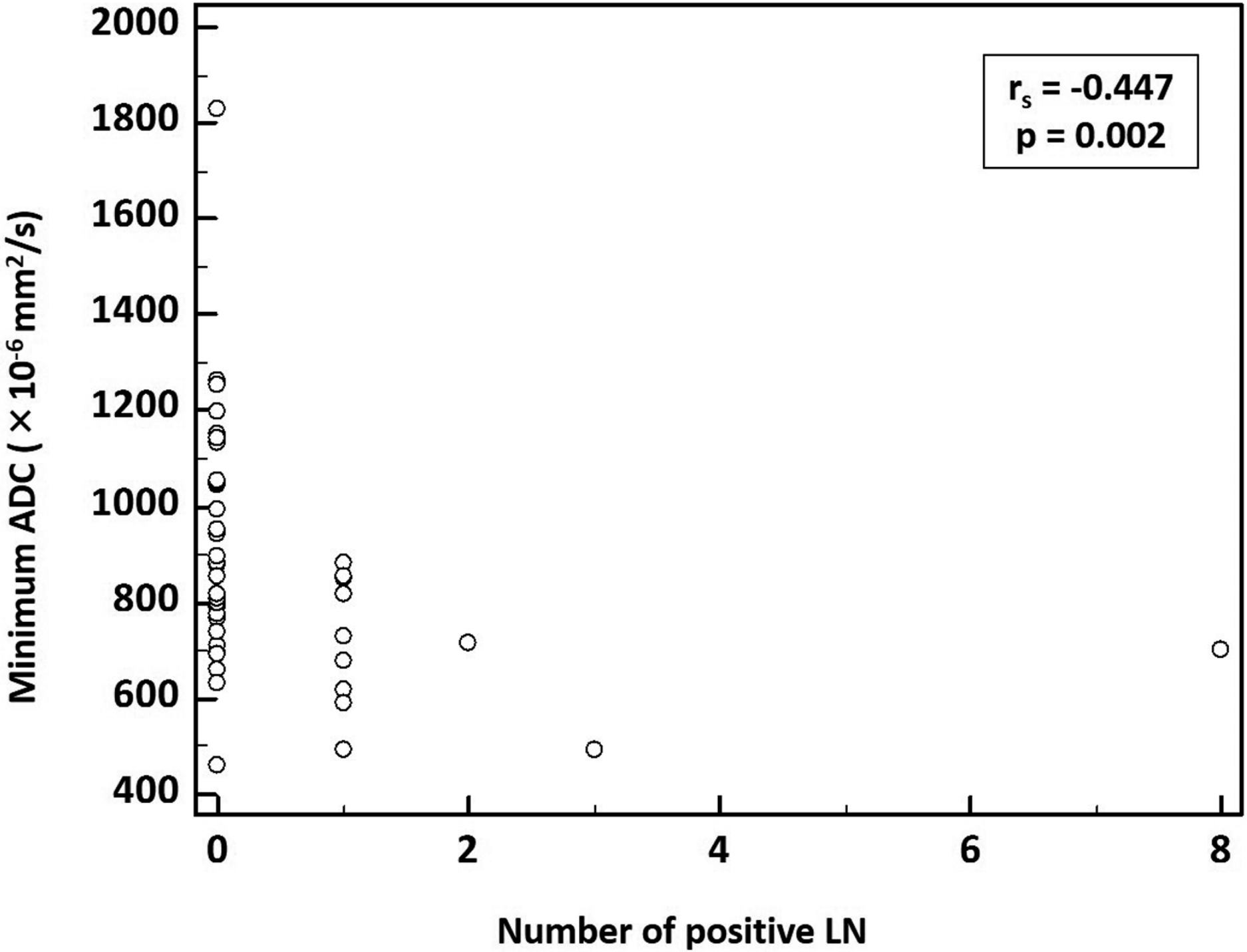

2000
1800
1600
1400
1200
1000
800
600
400
Minimum ADC (× 10-6 mm2/s)
0
2
4
6
8
Number of positive LN
rs = -0.447
p = 0.002

Table 1: Comparison of clinical and histopathological characteristics between axillary lymph node (LN) positive and negative lesions

	LN positive (n = 12)	LN negative (n = 32)	p-value
Age (years) (range)	54.6 ± 9.1 (42-79)	61.2 ± 9.6 (40-71)	0.059
Menopausal state			0.422
Premenopausal	4 (33.3%)	6 (18.8%)	
Postmenopausal	8 (66.7%)	26 (81.2%)	
Tumor size† (mm) (range)	21.2 ± 8.4 (9-35)	12.8 ± 7.4 (2-30)	0.004*
Histology			1.000
IDC‡	10 (83.3%)	25 (78.1%)	
Others	2 (16.7%)	7 (21.9%)	
Lymphovascular invasion			0.011*
Positive	5 (41.7%)	2 (6.3%)	
Negative	7 (58.3%)	30 (93.7%)	
Histological grade			0.135
1	6 (50%)	25 (78.1%)	
2	6 (50%)	7 (21.9%)	
ER†† (%) (range)	95.8 ± 9.0 (70-100)	97.0 ± 6.8 (70-100)	0.781
Ki-67 (%) (range)	9.6 ± 2.1 (6.8-12.6)	6.2 ± 3.8 (0.3-13.1)	0.006*

Quantitative data are presented as the mean ± standardized deviation.

*A p-value < 0.05 was considered to be statistically significant.

†Tumor size was measured by the largest diameter of the invasive component on the pathological specimen

‡IDC: invasive ductal carcinoma

††ER: estrogen receptor