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Role of DWI assessing nodal involvement and response to neoadjuvant chemotherapy in advanced breast cancer

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Abstract. – OBJECTIVE: To explore the role of diffusion-weighted imaging (DWI) in the staging of axillary lymph nodes and the restaging after neoadjuvant chemotherapy (NAD) in advanced breast cancer.

PATIENTS AND METHODS: MRI examinations of forty-two patients diagnosed with advanced breast cancer addressed to NAD and axillary lymph node dissection (ALND) were reviewed. Apparent diffusion coefficients (ADC) of each visible node in DWI in the pathologic axilla (PA) and healthy axilla (HA) were measured at the time of diagnosis (t0) and after chemotherapy (t1); mean values of the ADC were calculated. Patients were classified as responders (R), non-responders (NR), macrometastasis (MA), micrometastasis (Mi).

RESULTS: Mean ADC was 0.92 ± 0.07 x 10^{-3} mm^2/sec at t0 and 0.97 ± 0.06 x 10^{-3} mm^2/sec at t1 (p = 0.284) in PA, 0.89 ± 0.06 x 10^{-3} mm^2/sec at t0 and 0.92 ± 0.06 x 10^{-3} mm^2/sec at t1 (p = 0.403) in HA, 0.95 ± 0.111 x 10^{-3} mm^2/sec at t0 and 0.95 ± 0.14 x 10^{-3} mm^2/sec at t1 (p = 0.954) in R group, 0.90 ± 0.09 x 10^{-3} mm^2/sec at t0 and 0.97 ± 0.07 x 10^{-3} mm^2/sec at t1 (p = 0.085) in NR group, 0.86 ± 0.10 x 10^{-3} mm^2/sec at t0 and 0.99 ± 0.09 x 10^{-3} mm^2/sec at t1 (p = 0.055) in MA, and 0.99 ± 0.23 x 10^{-3} mm^2/sec at t0 and 0.95 ± 0.15 x 10^{-3} mm^2/sec at t1 in Mi (p = 0.667).

CONCLUSIONS: Mean ADC between PA and HA, R and NR, MA and Mi did not significantly differ at t0 and t1 (p > 0.05). Variation in mean ADC between t0 and t1 was not significant in all groups (p > 0.05), except for a trend toward significance (p = 0.055) in MA. DWI has a potential role in restaging of macrometastatic axillary nodes after NAD.

Key Words:
DWI, MRI, Lymph nodes, NAD, Breast cancer.

Introduction

According to the NCCN 2016 guidelines, neoadjuvant chemotherapy for breast cancer is indicated for stages IIA, IIB and IIIA (T3, N1, M0) who fulfill criteria for breast conserving surgery except for tumor size, or for inoperable or locally advanced non-inflammatory breast cancer (stages IIIA, IIIB and IIIC). Rates of locoregional recurrence are higher in patients who fail to achieve a pathologic complete response to neoadjuvant chemotherapy than in those who do[1]. Mamounas et al[2] have demonstrated that the presence of positive nodes after neoadjuvant therapy is the strongest predictor of the risk of locoregional recurrence at ten years and is a better predictor than presenting stage of disease or the presence of residual disease in the breast.

Monitoring of treatment response is important since discontinuation of inactive therapy in the event of disease progression avoids patient's exposure to potentially toxic therapy[3].

Breast MRI is the gold standard technique for the assessment of response to neoadjuvant chemotherapy in advanced breast cancer, since it best evaluates residual disease and assists in the planning of surgical treatment[4-6]. Then restaging of the axilla is not a current indication for breast MRI, since it has shown 59% sensitivity, 61% specificity, 43% positive predictive value and 75% negative predictive value when morphologic criteria are considered, thus resulting inadequate to preclude surgical axillary staging[7,8]. The utility of diffusion-weighted imaging (DWI) has been demonstrated for the assessment of response to chemotherapy in primary breast lesions, with a significant inverse correlation between mean apparent diffusion coefficient (ADC) increase and pathologic response[9]. Many works in literature have explored the utility of DWI in assessment of nodal status in pathologic axilla at the time of the diagnosis, reporting different cut-off values of

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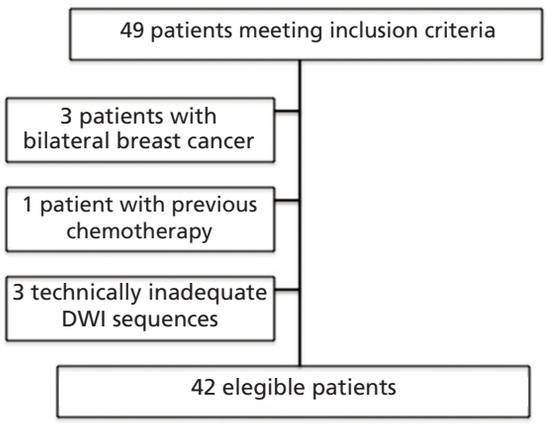

Figure 1. Study flow chart.

ADC and variable diagnostic performance[10-18] but, to the best of our knowledge, possible role of DWI in the restaging of axillary lymph nodes after neoadjuvant chemotherapy has not been investigated yet.

The aim of this study is to establish a possible relation between mean ADC values, number (N) of visible axillary nodes in DW imaging and nodal status at diagnosis and after neoadjuvant chemotherapy in advanced breast cancer.

Patients and Methods

Study Population

Forty-nine consecutive patients diagnosed with advanced breast cancer and addressed to neoadjuvant chemotherapy between January and July 2010 were evaluated. Patients included in this study had pathology proven (fine needle aspiration cytology) axillary node metastases at diagnosis. All patients underwent baseline and post-chemotherapy breast MRI examinations, including DWI sequences, followed by breast surgery with complete axillary lymph nodes dissection at our institution. Exclusion criteria were: previous chemotherapy and/or breast surgery, evidence of bilateral disease, motion artifacts or incomplete inclusion of the axilla in the field of view (FOV) of DWI sequences. Population selection and exclusion criteria are illustrated in Figure 1. As a result, the final study cohort was made of forty-two patients (age range 30-75 years; mean age 46.8 ± 10.5 years). Patients' demographics and tumor characteristics are shown in Table I. Surgical specimens' histopathology of complete axillary lymph node dissection was considered as the reference standard for the assessment of response to neoadjuvant treatment; accordingly, patients were classified as "responders" (R) and "non-responders" (NR) based on the evidence of metastatic cells. Although there is no current consensus on the pathologic definition of response to chemotherapy in axillary nodes, our NR group was further divided in "macrometastasis" (MA) and "micrometastasis" (Mi) for lesions measuring more or less than 2 mm, respectively.

This work was approved by our institutional Review Board and was conducted in accordance to the Declaration of Helsinki.

Imaging Protocol

Patients addressed to neoadjuvant chemotherapy routinely undergo breast MRI at our institution before the start of chemotherapy (t0), when approximately half of the course of chemotherapy has been administered, and fifteen days after the final course of chemotherapy (t1) to evaluate residual disease[4]. A written informed consent signed by each patient was obtained before the examinations. For women at reproductive age, the examination was performed between days seven and fourteen of the menstrual cycle, as appropriate. All patients were scanned in the prone position using a 1.5 T MRI scanner (Signa Excite; GE Medical System, Milwaukee, WI, USA) with a 4-channel bilateral breast coil. For contrast administration, an intravenous cannula was placed in the cubital vein just before the investigation. During the examination, contrast agent (gadopentetate dimeglumine) was injected at a dose of 0.1 mmol/kg using a power injector at a flow rate of 2 mL/s, followed by a 20 mL saline flush. The following sequences were acquired:

– *STIR (short time inversion recovery) axial sequence* [repetition time (TR) = 5900, echo time (TE) = 68, echo train length (ETL) = 17, bandwidth 41-67, 480×320 matrix, thickness=4 mm, 0 interval, field-of-view (FOV) = 32-34 cm, number of excitation (NEX) = 1-2].
– *DWI axial sequence* [TR = 5150, TE = min, frequency-phase 96 × 96, matrix 96 × 96, thickness = 4 mm, 0 interval, FOV = 32-34 cm, NEX = 6]. DWI was acquired before dynamic sequences with a spin echo EPI (echo-planar imaging) sequence in the axial plane. Sensitizing diffusion gradients were applied sequentially in the x-, y-, and z-directions with b-values of 0 and 1000 s/mm^2.

Table I. Patients' demographics and tumor characteristics. ALND: axillary lymph node dissection; SN: sentinel lymph node biopsy; PA: pathologic axilla; HA: healthy axilla. Results are shown in (n).

Patients		42	
Patients' age (years)			
	Range	30-75	
	Mean	46.8±10.5	
Axillary surgery	**ALND**	36	
	SN + ALND	5	
Responders (R)		15	
Non responders (NR)		27	
Macrometastasis (MA)		20	
Micrometastasis (Mi)		7	
Axillae		**84**	
Total lymph nodes		**630**	
	t0		**t1**
PA lymph nodes	199		158
HA lymph nodes	137		136
Total number of tumors		**42**	
T stage	**t0**		**t1**
T0	-		2
T1	6		17
T1m	-		5
T2	11		11
T3	12		7
T4	13		0
N stage			
N0	-		15
N1	16		11
N2	19		12
N3	7		4
Histology			
Ductal carcinoma in situ	36		
Lobular invasive carcinoma	5		
Tubular carcinoma	1		
Tumor grade			
G1	5		
G2	16		
G3	21		

– *Three-dimensional (3D) FSPGR (Fast Spoiled Gradient Echo) coronal sequence* [FA (flip-angle) = 15°, TR < 30 ms, TE < 5 ms, NEX = 0.5, thickness = 2-3 mm, 0 interval, 320×320 matrix, FOV = 34-38 cm] before and five times after intravenous contrast agent administration.
– *3D FSPGR sagittal fat-sat post-contrast sequence* [TR < 30, TE < 5, FA = 15°, 288 × 288 matrix, thickness = 2-3 mm, 0 interval, FOV = 22-26 cm, NEX= 2].
– *3D FSPGR axial fat-sat post-contrast sequence* [TR < 30, TE < 5, FA = 30°, 512 × 256 matrix, thickness = 2-3 mm, 0 interval, FOV = 34-38 cm, NEX = 2].

Image Analysis

Paired t0 and t1 MRI examinations were retrospectively reviewed for each patient in consensus by two radiologists with six and ten years of experience in breast MRI. Readers were blinded from the final pathology results of axillary lymph node dissection.

DW images were transferred to a workstation (Advantage Windows 4.1) and post-processed using the "Functool" program, in order to obtain ADC maps. We stated that the pathologic axilla (PA) was the ipsilateral to the breast cancer, while the healthy axilla (HA) was the contralateral one. Each lymph node was detected as a focal hyperin-

tensity in DWI; since inplane resolution and thickness of our DWI is not optimal and could lead to partial volume artifacts, with other structures such as vessels mimicking lymph nodes, we took T1w post-contrast images as anatomical references. A "node per node" analysis was made in both pathologic axilla (PA) and healthy axilla (HA); each node was contoured with a ROI (region of interest) to obtain the respective ADC value, including the whole lymph node and avoiding the surrounding fat tissue. Mean values of all lymph nodes ADC (mean ADC value) and a number of all detected lymph nodes for each axilla were recorded in a dedicated database.

Statistical Analysis

The normal distribution of continuous variables has been investigated using the Shapiro-Wilk normality test. Continuous variables following a normal distribution are presented as mean ± standard deviation (SD); variables with a skewed distribution are reported as median and interquartile range (IQR). Dichotomous variables are reported as frequencies and percentages. Continuous variables were compared among the PA and HA, R and NR, MA and Mi groups with the unpaired *t*-test or the Mann-Whitney U test, as appropriate. $p < 0.05$ was considered statistically significant.

Results

A total of 630 lymph nodes were analyzed, in particular, 357 pathologic nodes (199 at t0 and 158 at t1) and 273 benign nodes (137 at t0 and 136 at t1).

Median and IQR of number of lymph nodes was 4 (± 2) at t0 and 3 (± 3) at t1 ($p = 0.153$) in PA, 3 (± 3) at t0 and 3 (± 2.75) at t1 ($p = 0.952$) in HA. Difference in number of lymph nodes was statistically significant between PA and HA at t0 ($p = 0.017$), and became not significant at t1 ($p = 0.368$). Mean ADC value was $0.92 \pm 0.07 \times 10^{-3}$ mm²/sec at t0 and $0.97 \pm 0.06 \times 10^{-3}$ mm²/sec at t1 in PA ($p = 0.284$), while it was $0.89 \pm 0.06 \times 10^{-3}$ mm²/sec at t0 and 0.92 ± 0.06 × at t1 in HA ($p = 0.403$). In PA, mean ADC value was $0.95 \pm 0.111 \times 10^{-3}$ mm²/sec at t0 and $0.95 \pm 0.14 \times 10^{-3}$ mm²/sec at t1 ($p = 0.954$) in R group, while it was $0.90 \pm 0.09 \times 10^{-3}$ mm²/sec at t0 and $0.97 \pm 0.07 \times 10^{-3}$ mm²/sec at t1 ($p = 0.085$) in NR group. Mean ADC value was $0.86 \pm 0.10 \times 10^{-3}$ mm²/sec at t0 and $0.99 \pm 0.09 \times 10^{-3}$ mm²/sec at t1 ($p = 0.055$) in MA group, while it was $0.99 \pm 0.23 \times 10^{-3}$ mm²/sec at t0 and $0.95 \pm 0.15 \times 10^{-3}$ mm²/sec at t1 in Mi group ($p = 0.667$). At t0 and t1, respectively, not statistically significant difference was registered in mean ADC value between HA and PA ($p = 0.562$ and $p = 0.363$, respectively), R and NR groups ($p = 0.402$ and $p = 0.703$, respectively), and MA and Mi groups ($p = 0.300$ and $p = 0.608$, respectively). Results are summarized in Tables II and III. Examples of imaging processing in two patients are shown in Figures 2 and 3, with histopathology lymph nodes sections.

Discussion

In this work, we examined the potential role of some lymph nodes and DWI in the staging of the axilla and in restaging after neoadjuvant chemotherapy in advanced breast cancer.

Table II. Number (N) of lymph nodes and mean ADC values compared between baseline (t0) and after chemotherapy (t1) in pathologic axilla (PA), healthy axilla (HA), "non responders" (NR), "responders" (R), "macrometastasis" (MA) and "micrometastasis" (Mi). All ADC values are expressed as $\times 10^{-3}$ mm²/sec.

	t0	t1	*p*
N PA	4 (±2)	3 (±3)	0.153
N HA	3 (±3)	3 (±2.75)	0.952
PA	0.92 ± 0.07	0.97 ± 0.06	0.284
HA	0.89 ± 0.06	0.92 ± 0.06	0.403
NR	0.90 ± 0.09	0.97 ± 0.07	0.085
R	0.95 ± 0.11	0.95 ± 0.14	0.954
MA	**0.86 ± 0.10**	**0.99 ± 0.09**	**0.055**
Mi	0.99 ± 0.23	0.95 ± 0.15	0.667

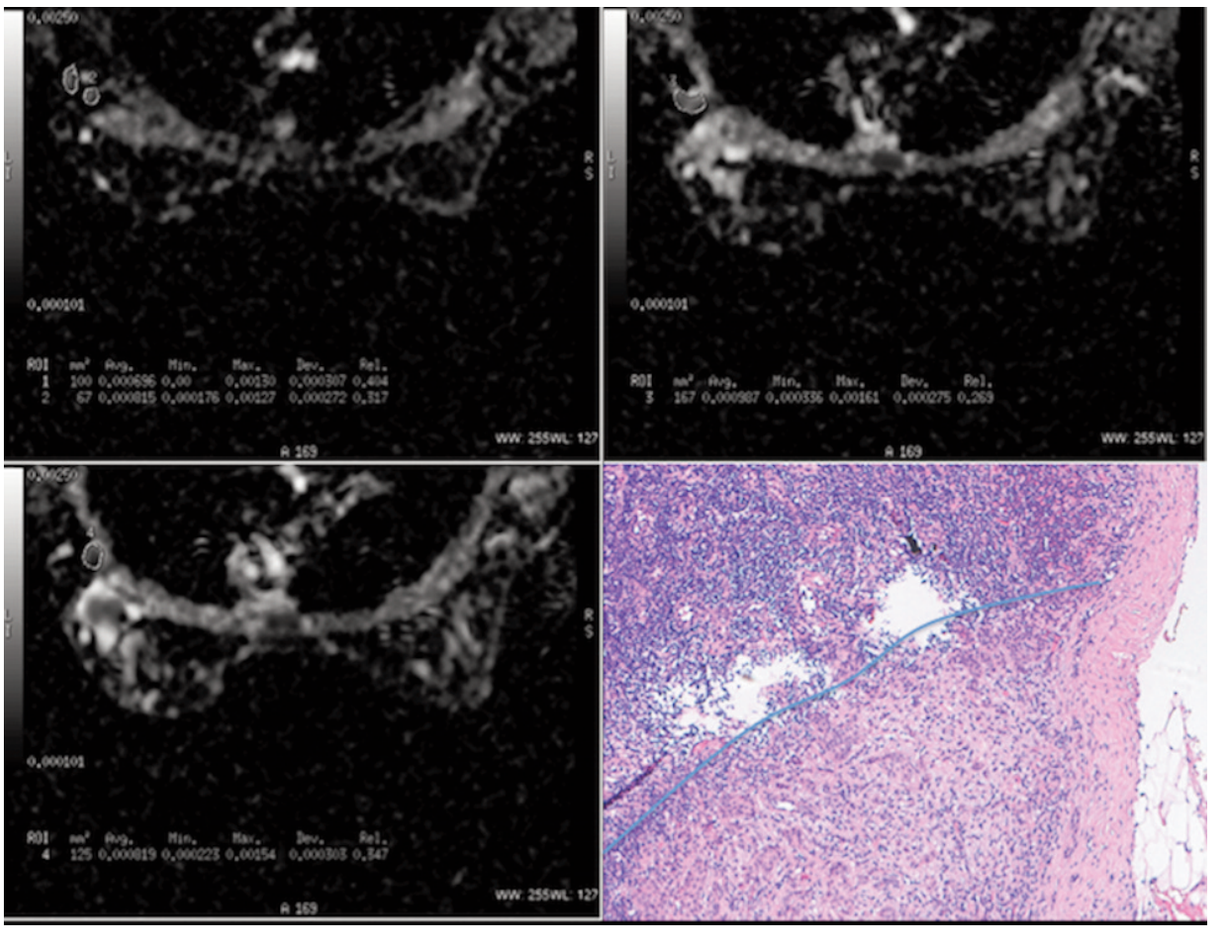

Figure 2. Patient with nodal macrometasis after neoadjuvant chemotherapy. Mean ADC value of lymph nodes in pathologic axilla before chemotherapy (0.82 × 10^{-3} mm^2/sec) and a lymph node section stained with hematoxylin-eosin depicting macrometastasis (under the blue line) are shown in ***(a)***. An increase of mean ADC value in the pathologic axilla (0.97 × 10^{-3} mm^2/sec) after chemotherapy, and a lymph node section with residual metastatic deposits in an area of reactive stromal changes are shown in ***(b)***.

Continued

Table III. Number of lymph nodes (N) and mean ADC values compared between pathologic axilla (PA) and healthy axilla (HA), non responders (NR) and responders (R), macrometastasis (MA) and "micrometastasis" (Mi) at t0 (baseline) and t1 (end of chemotherapy). All ADC values are expressed as × 10^{-3} mm^2/sec.

	t0	*p*	t1	*p*
N PA	4 (±2)	**0.017**	3 (±3)	0.368
N HA	3 (±3)		3 (±2.75)	
PA	0.92±0.07	0.562	0.97±0.06	0.363
HA	0.89± 0.06		0.92±0.06	
NR	0.90±0.09	0.402	0.97±0.07	0.703
R	0.95±0.11		0.95±0.14	
MA	0.86±0.10	0.300	0.99±0.09	0.608
Mi	0.99± 0.23		0.95 ± 0.15	

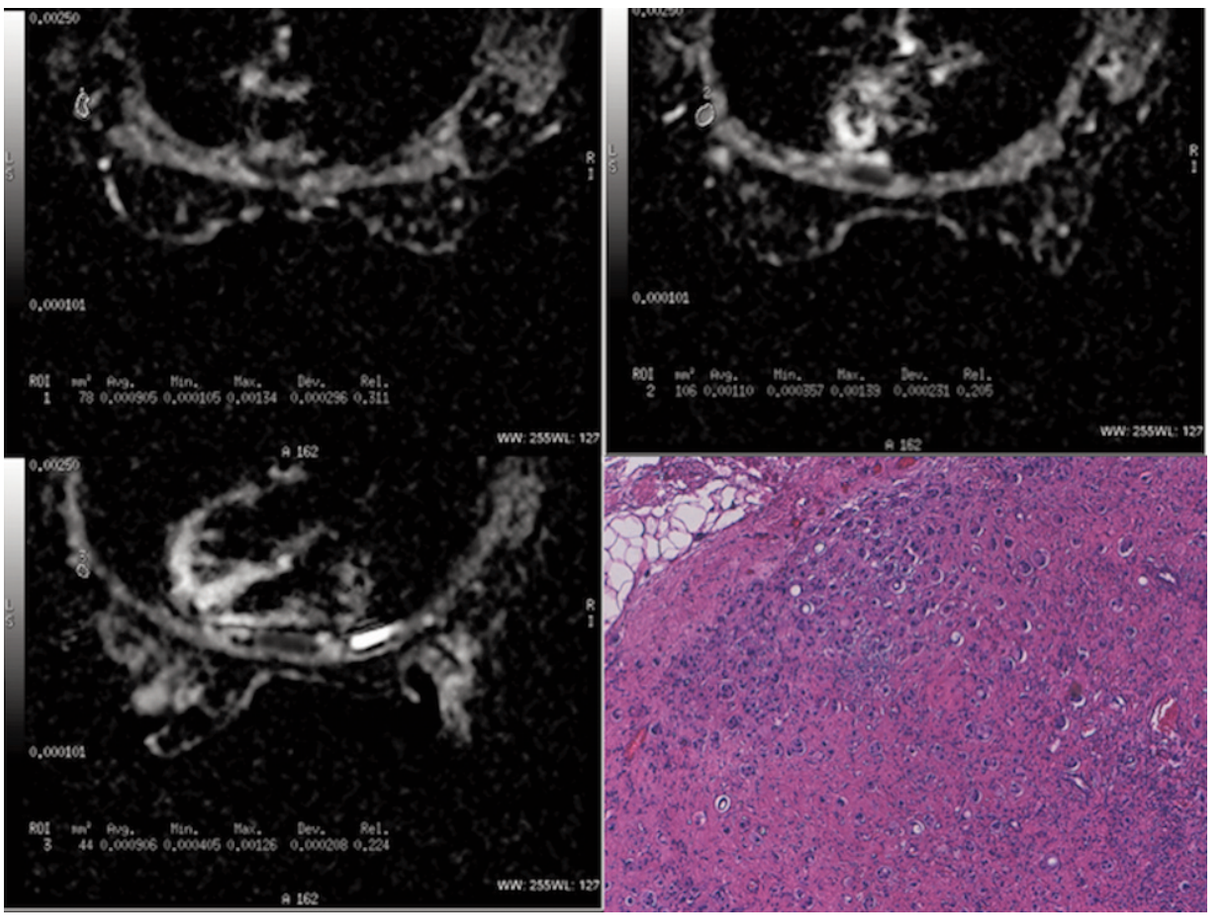

Figure 2. *(Continued).* Patient with nodal macrometasis after neoadjuvant chemotherapy. Mean ADC value of lymph nodes in pathologic axilla before chemotherapy (0.82×10^{-3} mm²/sec) and a lymph node section stained with hematoxylin-eosin depicting macrometastasis (under the blue line) are shown in ***(a)***. An increase of mean ADC value in the pathologic axilla (0.97×10^{-3} mm²/sec) after chemotherapy, and a lymph node section with residual metastatic deposits in an area of reactive stromal changes are shown in ***(b).***

According to our results, axillae involved with metastatic disease are more likely to have a larger number of lymph nodes than healthy axillae at the time of diagnosis, while this difference is not significant after the end of chemotherapy.

Our data showed an overall uniformity in mean ADC values between pathologic and healthy axillae at the time of diagnosis, demonstrating that this parameter is not useful in assessing pathologic lymph node involvement. In pathologic axillae there was not a significant difference in mean ADC values between responders and non-responders, both before and after chemotherapy; thus, this parameter is not predictive nor indicative of a response to neoadjuvant treatment. Since we are aware that different cellular amount between macrometastasis and micrometastasis could differently affect ADC values among pathologic lymph nodes, we further stratified pathologic axillae in these two groups. We found that axillae involved with residual macrometastasis have a higher mean ADC value at the end of chemotherapy in comparison to the baseline examination, with a trend toward significance ($p = 0.055$). According to our results, in clinical practice, a significant increase in mean ADC value of pathologic axilla after neoadjuvant chemotherapy could be considered as an indicator of residual macrometastases; anyways the cut-off value of a significant variation could not be established in this study due to the small population examined. Our data could be explained by the pathologic changes that occur microscopically in lymph nodes after chemotherapy. Before

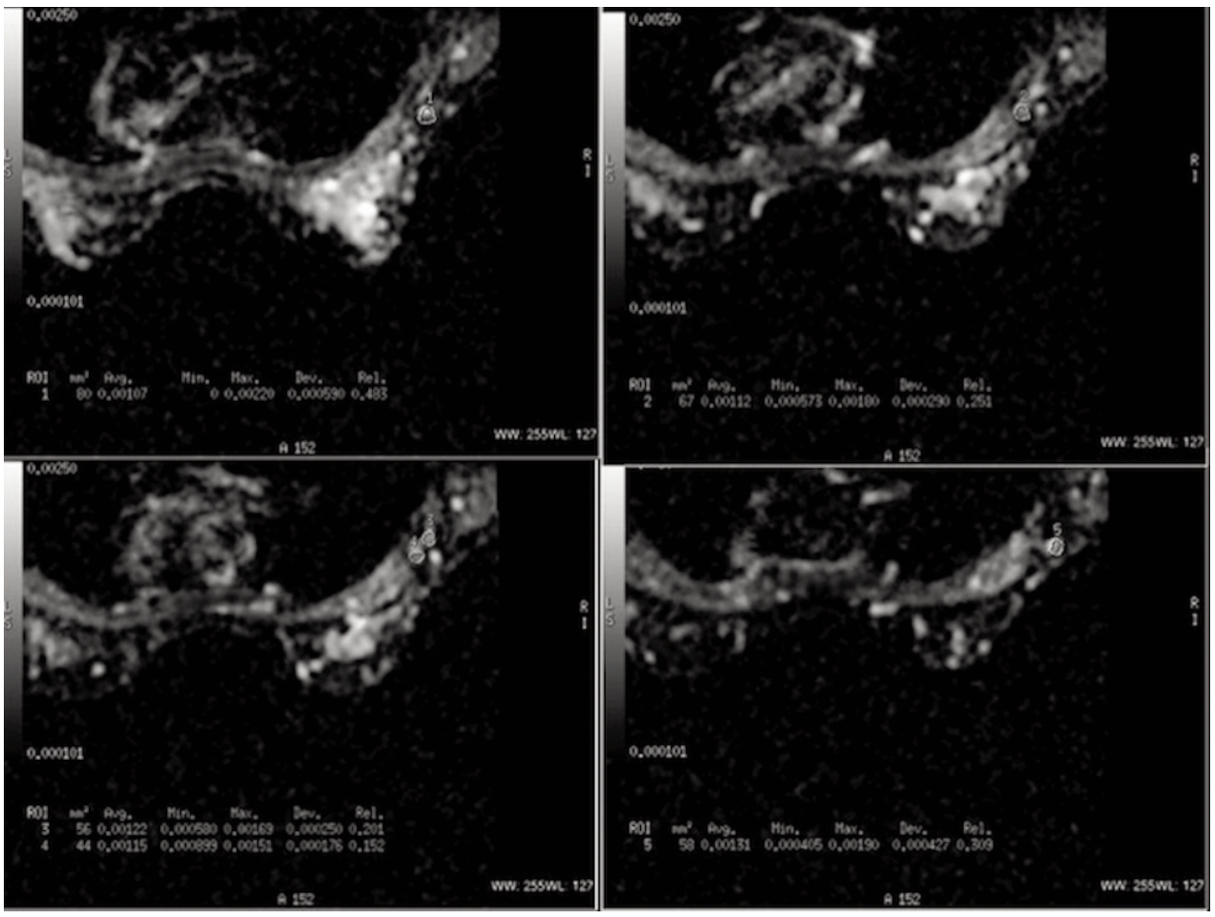

Figure 3. Patient with nodal micrometastases after neoadjuvant chemotherapy. Figure ***(a)*** shows mean ADC value of lymph nodes in pathologic axilla before chemotherapy (1.74×10^{-3} mm²/sec); in ***(b)***, after chemotherapy, a decrease of axillary lymph nodes mean value can be appreciated (1.01×10^{-3} mm²/sec).

Continued

chemotherapy, metastatic cells are located within the numerous and cluttered lymphocytes that normally occupy the lymph nodes cortex. Therefore, we suppose that they cannot significantly affect the ADC value at the baseline examination. After chemotherapy, fibrosis with a variable amount of residual metastatic cells replaces the site of previous metastases, depending on the response to treatment: the larger is the size of metastases, the more conspicuous is the entity of post-chemotherapy changes, which are more evident for macrometastases than for micrometastases, and do not affect significantly the healthy lymph nodes. The entity of these changes reduces lymph nodes cellularity and, accordingly, the ADC value increases.

Some studies in the literature have investigated the role of DWI in the assessment of nodal status in advanced breast cancer[10-18], whose main results are reported in Table IV. Most of these researches reported different results from ours; in particular, a lower ADC was reported for pathologic nodes in comparison to benign nodes. In most of these studies, ADC analysis was performed only on the most suspicious lymph node on the base of morphologic criteria, and this different approach could explain such different results from our work[10-16]. In the two available studies in which a node per node analysis was performed, different results were reported. In particular, He et al[17], which used b values of 500 and 800, demonstrated that metastatic nodes have a lower ADC than benign nodes; however, the small number of metastatic lymph nodes regarding the overall study population was described as a limitation by the authors.

On the other hand, a node per node analysis performed by Schipper et al[18] with a high field

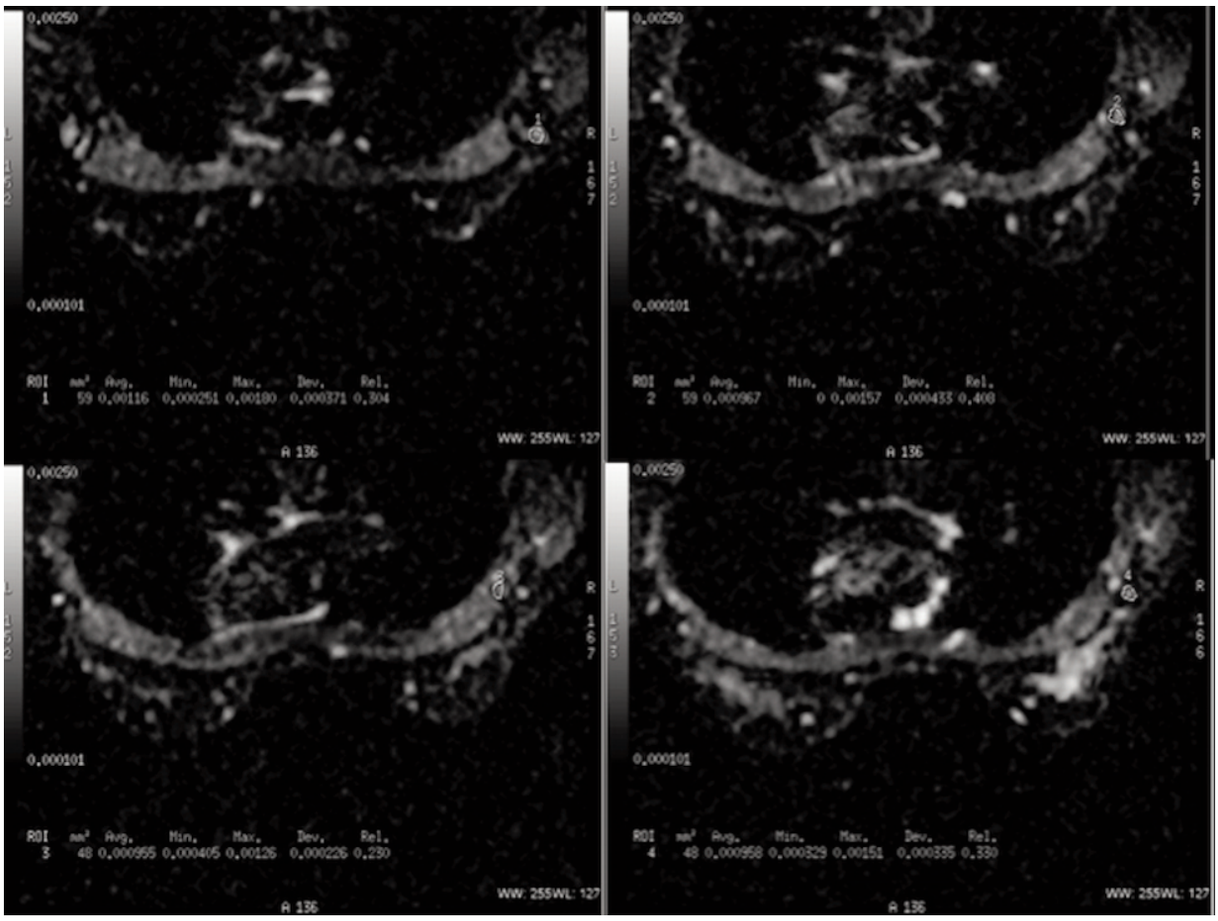

Figure 3. *Continued.* Patient with nodal micrometastases after neoadjuvant chemotherapy. Figure ***(a)*** shows mean ADC value of lymph nodes in pathologic axilla before chemotherapy (1.74×10^{-3} mm²/sec); in ***(b)***, after chemotherapy, a decrease of axillary lymph nodes mean value can be appreciated (1.01×10^{-3} mm²/sec).

scanner (3T) and dedicated protocols for the axilla both with T2 weighted sequences and DWI, who reported a non-significant difference between mean ADC of metastatic and benign lymph nodes, in agreement with our results. To the best of our knowledge, there are no available papers investigating a possible role of DWI in the restaging of the axilla after neoadjuvant chemotherapy; moreover, previous neoadjuvant chemotherapy was an exclusion criterion in most of the above-mentioned studies.

Despite discouraging findings about DWI, non-morphologic MRI techniques reflecting microscopic changes in lymph nodes are worth being further investigated. In particular, the possible application of USPIO particles, which showed a reported mean sensitivity of 98% and mean specificity of 96% for detection of axillary metastases in a study conducted in newly diagnosed breast cancers[19], is worth to be investigated in the setting of neoadjuvant chemotherapy as well. According to the results of recent surgical trials[20], axillary node dissection can be omitted under certain preconditions (tumors smaller than 5 cm, cN0, M0, planned breast whole irradiation for breast conservative surgery) in patients with affected sentinel lymph nodes without altering local recurrence rate significantly. Thus, the role of radiologists in the staging of the axilla would consist of identifying the presence of axillary metastases with a positive predictive value high enough to be useful to the surgeon in deciding when to proceed directly to ALND[21]. On the other hand, the applicability of the results of this trial are on debate[22,23] and still not considered in the set-

Table IV. Available studies results about baseline mean ADC values in benign and pathologic axillary nodes in comparison with our results. All ADC values are expressed as $\times 10^{-3}$ mm^2/sec.

Authors	ADC benign	ADC malignant	p
Fornasa et al[10]	1.494; range: 0.60-2.50	0.878; range: 0.30-1.20	< 0.001
Kim et al[11]	1.270 ± 0.32	0.910±0.29	< 0.001
Chung et al[12]	1.04	0.69	< 0.001
Luo et al[13]	1.043 ± 0.257	0.787 ± 0.145	< 0.05
Scaranelo et al[14]	0.720 ± 0.173	0.673 ± 0.500	< 0.05
Rautianen et al[15]	1.100-1.225	0.663-0.676	< 0.001
Kamitani et al[16]	0.92 ± 0.22	1.08 ± 0.18	0.004
Ni He et al[17]	b = 500, 1.7651 [0.3509]	b = 500, 1.3693 [0.1766]	0.000
	b = 800, 1.5513 [0.3134]	b = 800, 1.1822 [0.1244]	
Schipper et al[18]	0.754 (95% CI: 0.706, 0.801)	0.666 (95% CI: 0.524, 0.808)	0.219
	0.747 (95% CI: 0.701, 0.792)	0.712 (95% CI: 0.570, 0.854)	0.590
Our results	**0.89 ± 0.06**	**0.92 ± 0.07**	**0.562**

ting of neoadjuvant chemotherapy[24]; in this particular setting studies in the literature have demonstrated a reduction in diagnostic performance of sentinel lymph node biopsy[25,28]. If the omission of axillary lymph node dissection will be considered also for patients who underwent neoadjuvant chemotherapy, new diagnostic techniques could be supportive in surgical planning, avoiding unnecessary axillary lymph nodes dissections.

There are some limitations in this work that should be acknowledged. First, we are aware that calculation of mean ADC value could have reduced any difference due to single lymph nodes ADC, and this could explain the non-significant differences between some groups. Also, small study population, mainly due to the exclusion of patients with technical artifacts in DWI sequences, which is a common issue in clinical practice, represents another limitation in our work. For this reason, we weren't able to calculate cut-off values in some lymph nodes for differentiation between PA and HA at t0, and in a variation of mean ADC between t0 and t1 for differentiation of "macrometastatic" from "micrometastatic" and benign lymph nodes. On the base of the changes observed after chemotherapy at histopathology, an increase of ADC level would be expected also for the responders group if were initially involved with macrometastases, but data about metastases size at the time of diagnosis were not available in our analysis. Also, we haven't performed intra- and inter-observer variability in measurements of ADC.

Conclusions

DWI is not useful in assessing nodal status in advanced breast cancer, while a number of lymph nodes are higher in axillae involved with metastases at diagnosis.

An increase of mean ADC which is close to statistical significance has been observed after neoadjuvant chemotherapy in lymph nodes with residual macrometastases; thus, DWI could be helpful in the restaging of the axilla after chemotherapy. Further researches with a prospective design and a larger study population are needed to confirm our findings.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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