IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 16, Issue 8 Ver. VII (Aug. 2017), PP 95-104
www.iosrjournals.org

Diffusion-Weighted MRI in Monitoring Locally Advance Breast Cancer Response to Neoadjuvant Chemotherapy

*Vahid Changizi[1], * Mohannad Ahmed Sahib[2], Zahra Tizmaghz[3]

[1]*Professor, Department of Technology of Radiology and Radiotherapy, Allied Medical Sciences School, Tehran University of Medical Sciences, Tehran, Iran.*
[2] *M.Sc. Researcher , Department of Technology of Radiology and Radiotherapy, Allied Medical Sciences School, international campus ,Tehran University of Medical Sciences, Tehran, Iran.*
[3]*M.Sc. Radiotherapy and neuroscience , Radiation oncology department of cancer Imam Khomeini hospital , Allied Medical Sciences School, Tehran University of Medical Sciences, Tehran, Iran.*
*Corresponding author: * Mohannad Ahmed Sahib*

Abstract :
Objectives *We have evaluated changes in tumor ADC on DWI values before and after Neoadjuvant Chemotherapy to predict the treatment response in LABC and to measure the response to NACT among patients with locally advanced breast cancers preoperatively.*
Materials and Methods *The following databases including Embase, the Cochrane library, MEDLINE, PubMed, Elsevier, Springer and free journals were searched via the search queries published until 1 July 2016. In order to have qualification for this study, we determined that a study should consist patients by newly diagnosed or recurrent, histologically proven breast cancer undergoing NACT who were imaged using MRI and predefined inclusion, extraction criteria and exclusion criteria.*
Results *In 18 studies, which were mainly various study designs, most repeatedly parameters on studied were tumor volume and diameter, apparent diffusion coefficient (ADC). Majority of included studies were of prospective design. Several studies showed pretreatment ADC can differentiation of responders tumor from non-responders to NAC; it is also leading to decide whether NAC is a valid therapeutic option. Many studies have shown up that successful treatment is reflected by an ADC values is increase , which is believed to be the consequence of cellular damage and necrosis and reported sensitivity ADC and specificity on diffusion-weighted MR imaging for early response monitoring. Tumor diameter, volume, parameters observed no significant difference was between responders tumor and non-responders in terms of mean pretreatment tumor sizes percentage decrease in tumor volume also diameter wasn't significant between responders and non-responders. At pretreatment and early response monitoring significant and nonsignificant changes for all parameters were observed for most of the imaging parameters.*
Conclusions *DWI has many advantages as a biomarker to predict and monitor NAC in LABC women as it provides early response indicators based on information on microstructural changes related to therapy effects with the passage of time that usually follow alterations in tumor size and the mean of apparent diffusion coefficient (ADC) respectively. Moreover, the indication on recognizing non-response earlier before treatment may encourage changing in therapeutic strategies to avoid toxicity, direct individualization of treatment and, consequently, enhance patients' outcome and increase overall survival.*
Keyword: - *Diffusion-Weighted MRI, Locally Advanced Breast Cancer (LABC), MR imaging, Neoadjuvant chemotherapy*

Date of Submission: 15 -07-2017 Date of acceptance: 23-08-2017

I. Introduction

Locally advanced breast cancer (LABC) contains huge primary tumors (>5 cm in diameter). These are implicated in different places into body such as skin and/or the chest wall. Several characteristics of tumors like fixed or matted axillary lymph nodes (T3/T4, N2) plus and those that involve the ipsilateral subclavicular and supraclavicular lymph nodes are existed. The mentioned patients have need of neoadjuvant combined chemotherapy in order to lessen the stage of tumors previous to surgical operation[1]. The objective of neoadjuvant chemotherapy in LABC is diminishing the size of the primary tumor to make breast conservation surgery possible and ameliorate the survival rate through eliminating micrometastatic disease[2,3]. It is necessary to have quick response tumors to NACT since its outcome goes back to the favorable management and steer clear of maintenance of toxic therapy in non-responding patients. To notify, magnetic resonance imaging (MRI)

is well thought-out the optimum option in weighing up the tumor and its reply to the administered treatment because of its higher precision compared to conventional processes of physical examination, mammography, and sonography[4].

In order to identify an untimely response tumors to NAC, there are three main methods in qualitative monitoring approach : dynamic contrast-enhanced MRI (DCE-MRI), MR spectroscopy (MRS), and diffusion-weighted imaging (DWI). The DCE-MRI detects drug-induced alters in tumor vascularity, Contrast Enhanced MRI (CE-MRI) afford precise measurement of the tumor size and volume, which are the most common pointers used for evaluating tumor response after NACT[5]. We could show the sensible diminution of tumor volume due to one cycle of NACT and with reflection or presentation of stable condition. On the other hand, there are restrictions with by means of CE-MRI alone in the evaluation of reaction to treatment[6]. There are a variety of factors which could bring about overestimation and underestimation of tumor size calculated by CE-MRI as well. CE-MRI may overvalue tumor size owing to surrounding sclerosis or necrosis, multiple scattered lesions or foci, reactive inflammation origined by tumor response, and associatedwith ductal carcinoma in situ (DCIS). A number of chemotherapy agents contain antivascular effect which are capable to add DCIS module (which may be complicated to classify by CE-MRI), and incomplete amount effects of extremely tiny foci of remaining disease may cause to underrate of tumor size by CE-MRI [7], whereas MRS shows changes in the water/fat ratio and concentrations of choline-containing composites in tumors[8].

Diffusion-weighted imaging (DWI) is such a modern tool in MRI machinery, presenting in vivo alterations images of biological tissues weighted with the local microstructural properties of water diffusion. DWI is stand on the diffusive characteristics of water molecules and reproduce their random motion resulting from thermal agitation (Brownian motion). This method has potential to supply information for local tissue style and show an untimely detection of abnormality and cellularity which are index of tumor grade. It is recognized for the functional properties of tissues (for example, biochemistry and metabolism, vascularity, oxygenation levels, cellularity and levels of gene expression)[9,10].

Here, we present some properties of two types of water molecules. To notify, random movement in biological tissue is considerable. Slow movement and low diffusion plus high diffusion molecules, whereas the former present attachment to large molecules and is stuck in cell membrane, the later demonstrate extracellular activity[11]. That's why, diffusion weighted MR imaging should be responsive to more than a few physiologic and morphologic properties of tissue that are connected to the slow or fast diffusion of water molecules. Cell density and tissue viability, as well as modifications in tissue in reaction to diverse treatments are some of these exclusivity. Provided information about the slow diffusing water treatment by high-*b*-value diffusion-weighted MR imaging is capable to improve the sensitivity of the method for finding, in early treatment steps of fairly small effects including modified permeability of cell membranes, cell swelling, and early cell lysis[12].

Apparent diffusion coefficient (ADC) rate in square millimeters per second is utilized as a way of diffusion quantification, which characterize the regular area coated by a molecule per unit time[13]. The apparent diffusion coefficient (ADC) is measured from various images with diverse degree of diffusion weighting (b-values), and imitate the level of restricted water diffusion. tumor and intracellular structure, The increased levels of ADC is desired when an efficient treatment is done and has led to modifications in and is associated with water diffusion devoid of any necessitate for injected contrast material. Nevertheless, the mean change of ADC had great levels in responders than in non-responders subsequent to the entire cycles of NACT in patients with breast cancer[14-18].

In order to screen and categorizing breast abnormalities, imaging from mentioned tissue is required.

DWI has numerous beneficials as a biomarker as it makes available information on microstructural alterations linked to treatment effects over time that typically come first changes in size, and no ionizing radiation or injection of isotope or any other contrast medium is compulsory. Moreover, the achievement time of DWI is relatively short, the process is straightforwardly repeatable for providing quantitative information and this method is magnetic field independent[19]. In this research, we aimed to evaluate modifications in tumor ADC on DWI standards previous and after to Neoadjuvant Chemotherapy to prediction of treatment response in LABC and to measure the response of NACT amongst patients with locally advanced breast cancers preoperatively.

II. Materials And Methods

2.1. Literature Search

This study was accepted by the ethics committee of our institution in ‘‘March 2017 ’’. It included (18) articles successive female patients with locally advance breast cancer diagnosed. We performed this study for articles that specifically coped with the use of DW-MRI in patients with Locally Advance Breast Cancer for monitoring response to neoadjuvant Chemotherapy. The following databases, Embase, MEDLINE, Pubmed, the Cochrane library ,Elsevier, Springer and free journals were searched by the search queries: “breast cancer” “Locally Advance Breast Cancer OR LABC” AND “MRI OR magnetic resonance imaging” AND “diffusion

weighted imaging OR DWI" AND "Neoadjuvant Chemotherapy OR NACT" AND "monitoring and response" . Only original articles that performed (i.e. no reviews, brief communications or literatures to the editor) between the years 1990 to 2016 presented in English language relevant to our objectives were reflected for inclusion. These databases were additionally explored using the ''Related Articles'' function in PubMed. The same query was used to browse the web using scholar.Google.com. Moreover, the references of wholly retrieved articles were yourself searched for pertinent cross-references. Thereafter, all recovered articles were compared and from overlapping series of patients only the most recent publication was acknowledged. Studies found over these search terms were measured for potential admissibility by screening for significance on title and reading the abstracts first and then full text article and at that point inclusion then exclusion criteria was applied.

2.2. Inclusion and Extraction Criteria

Included articles were only those in which LABC DWI was achieved to judge response to NACT. In order to be eligible for this review, we defined that a study should comprise patients by newly diagnosed or recurrent, histologically proven breast cancer undergoing NACT who were imaged using MRI (i.e. least possible 1.5 T).

We did not omit studies if other imaging modalities were done parallel to DWI in order to assess treatment response. Subsequent to this initial assessment, the publications were summarized using a standard extraction form. The data was gathered through: first author, study design (retrospective or prospective), year of publication, population size, mean patient age and range, cancer type and stage at inclusion, cancer histology and imaging response assessment, whereas the extraction forms in consensus was recorded.

2.3. Exclusion Criteria

For the admitted articles, we excluded the following information: first articles were monitoring response to radiotherapy and some were excluded if the study outcome proved not to cover information on response appraisal by DWI. Data or part of data offered in more than one article (in this case, the article containing the latest and/or the most complete data was chosen) and animal studies, reviews, case report, letters, editorials, abstracts, comments, and in vitro studies and studies including less than 8 patients and articles deprived of satisfactory information.

2.4. Statistical Analysis

All reported P-values ≤ 0.05 were considered statistically significant. The huge differences among retrieved articles convinced us not to pool due to heterogeneity and utilize descriptive statistics in this review. We designated some variables to be considered while choosing the referenced articles for enrolling in this review; these variables were:

1. Article study type including clinical trial, systematic review, meta-analysis, RCT (Randomization control trial), case control, cross sectional and case report. Each study type has its own level of evidence. The higher level will go to RCT, systematic reviews and meta-analysis, whereas the subordinate one come to descriptive studies like cross sectional and case reports.
2. We considered the consequences of the patients in case of response to treatment by comparing ways of ADC existing in reviewed articles before and after NACT.

We looked up eligible articles, considered them according to study area of type, summarized their judgements in tables and compared different means of ADC on DWI values accessible in studied literatures. Proper statistical test was used when needed.

We discussed alteration in treatment response rates (percent) among reviewed studies and defined chief related features of the patients when existing.

III. Results

3.1. Study Selection

We gathered a total of 263 articles next to systematic search in scientific search engine, of which 53 were double in various searches, leaving 2, 10 studies later the primary search. By estimating the titles then abstracts, we found 98 articles to be potentially appropriate by considering the inclusion then exclusion criteria. Subsequent to measure the full context, 18 studies (table 2) encountered the inclusion criteria of having ADC values pre and post NAC as mean or percent changes. Likewise, eligible articles were acquiesced to further in depth reading, summarization and comparison in this study. (Figure 1) shows a more complete overview of the study selection process.

3.2. Study Description and Patients Characteristics

Of the 18 included studies in this research, 12 were prospective and six retrospective. A total of 627 patients were included in the studies (mean 43.8 patients per study). Median age of patients was 49.0 years (18

to 83 years). Among those patients, majority of LABC types were IDC and ILC. Studied lesions were staged I to IV according to WHO classification[20]. The features of included studies are registered in table (2). After the comprehensive search was accomplished and reference index were cross-checked, four studies were performed on a 3-T MRI scanner, one on both 3 and 1.5T scanners, and the left over studies on 1.5-T MRI scanners. In wholly studies, a commercially existing gadolinium-based enhance contrast agent was utilized for breast MRI at regular clinical management doses. Interestingly, there was a remarkable heterogeneity in breast stages cancer and subtypes, NCT regimens, and methods utilized for response assessment in imaging , histopathological and volumes investigates (Tables 1 and 2).

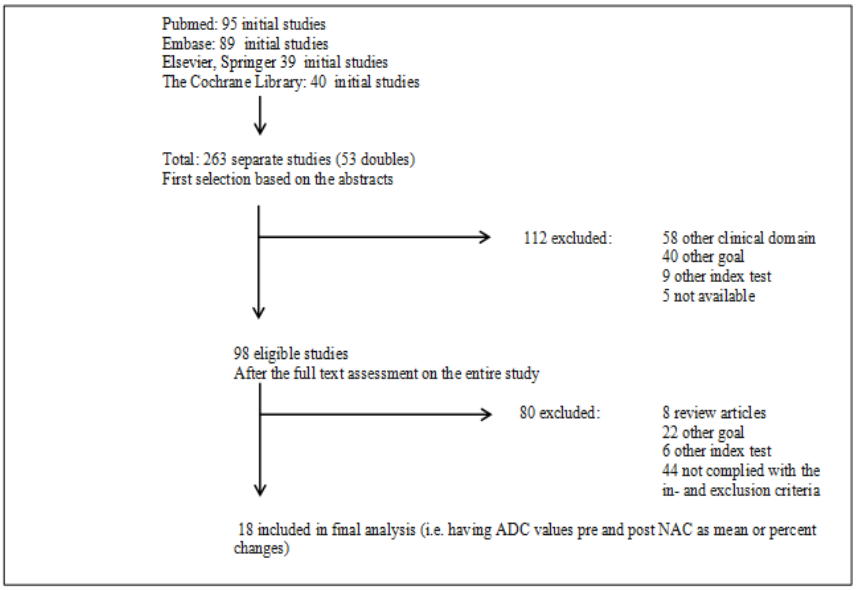

Fig.1 Detailed overview of study selection

3.3 Role of DWI in assessing and predicting response to NAC

We revised illegible 18 studies conducted in the past 25 years where data on exploring the role of DWI is available equally in monitoring and predicting response to treatments in LABC. Table 2 shows the foremost results of these studies regarding the role of pretreatment ADC values in predicting therapy response.

Table 1. Main characteristics of included studies

Author	Year	Study type	Patients No.	Age: Mean (±SD) OR Median (range)	Cancer type	Cancer stage
Li et al	2011	P	32	46 (25-63)	LABC	III
Yankeelov et al	2007	P	11	>18	IBC	II-III
Park et al	2012	R	34	44 (27-60)	IDC, MDLC, MC	-
Park et al	2010	R	53	43.7 (24-65)	IDC, MDLC, MC	II-III
Shin et al	2012	R	41	46 (24-68)	IDC,ILC	II-III
Woodharms et al	2010	P	69	-	IDC, ILC, MC, DCIS	-
Nilsen et al	2010	P	25	51 (37-72)	LABC	II-III
Fangberget et al	2011	P	31	50.7 (37-72)	IDC, ILC	II-III
Belli et al	2011	P	51	48.4 (26-66)	IDC, ILC	-
Iacconi et al	2010	P	21	50 (39-68)	IDC, ILC, MC, DCIS	-
Sharma et al	2009	R	56	48.5 (25-75)	IDC	II-IV
Pickles et al	2006	P	8	-	IDC	-
Iwasa et al	2014	R	24	54.3 (32-69)	-	I-IV
Jensen et al	2011	P	12	56.6 ± 11.6	IDC, ILC	III-IV
Kawamura et al	2011	P	12	54 (38-69)	LABC	II-III
Richard et al	2013	P	118	53.2 (23-83)	IDC, ILC	II-IV
An Y Y et al	2015	R	20	51.6 (29-69)	IDC, MC	II-III
Wilmes et al	2013	P	9	49 (24-66)	IDC	II-III

P = prospective; R= retrospective; LABC= locally advanced breast cancer; IDC= invasive ductal carcinoma; ILC= invasive lobular carcinoma; MC= mucinous carcinoma; MDLC=mixed ductal lobular carcinoma; DCIS=ductal carcinoma in situ

Table 2. Results for the prediction of response to therapy based on the ADC parameters value

Author	Year	Field strength (T)	Reference response evaluation	ADC mean ($\times10^{-3}$ mm^2/s) or % change		P value
				Pre-NAC	Post-NAC	
Li et al	2012	1.5	pCR on pathology	0.98±0.16	1.22±0.26	<0.001
Yankeelov et al	2007	1.5	pCR on pathology	1.61±0.22	2±0.6	<0.005
Park et al	2012	1.5	pCR on pathology	1.069	1.562	<0.001
Park et al	2010	1.5	pCR on pathology	1.036±0.015	1.524±0.046	<0.001
Shin et al	2012	1.5	pCR on pathology	0.83(0.77-0.87)	1.43(1.24-1.69)	0.014
Woodharms et al	2010	1.5	pCR on pathology	1.0 ±0.3	-	0.64
Nilsen et al	2010	1.5	Tumor volume	1.11±0.21	1.39±0.36	0.018
Fangberget et al	2011	1.5	pCR on pathology	1.1	1.7 (1-2.1)	0.022
Belli et al	2011	1.5	pCR on pathology	1.11±0.16	1.4±0.3	<0.001
Iacconi et al	2010	1.5	>65% Tumor volume reduction	0.99±0.27	1.26±0.39	0.024
Sharma et al	2009	1.5	Tumor volume	0.95±0.11	1.3±0.24	<0.001
Pickles et al	2006	1.5- 3	Tumor volume	1.08±0.19	1.37±0.24	0.004
Iwasa et al	2014	3	Tumor volume	1.006 (0.66-1.359	7.8%	0.016
Jensen et al	2011	3	Tumor volume	1.02±0.09	1.13±0.17	0.008
Kawamura et al	2011	3	Tumor volume	-	-5.2-23%	<0.005
Richard et al	2013	1.5	pCR on pathology	1.06±0.143	1.227±0.271	0.047
An Y Y et al	2015	3	pCR on pathology	-	32.8%	0.67
Wilmes et al	2013	1.5	>65% Tumor volume reduction	HR 1.3±0.34 STD 1.37±0.3	1.49±0.37 1.6±0.4	0.03 0.01

ADC= apparent diffusion coefficient; pCR= pathological complete response

Iwasa et al.[21] found a large correlation between percent ADC change and tumor response rate to NAC (r=0.59, p=0.016). Breast cancer lesions with high percent ADC change values responded to NAC, while those with low values did not. Mean percent ADC change was 7.8 % (-33.8% ± 24.13%) prior and post NAC.

There were nine studies[14,17,23-28] using values ADC on DWI in predicting treatment response in patient with LABC undergoing NAC, concluded that DWI sensitivity was 93% (82–97% at 95% CI) and specificity was 82% (70–90% at CI 95%) in predicting pathologic complete response . **Park *et al*.**[16] recommended that the best pretreatment ADC value was 1.17×10^{-3} mm2/s (at b = 750 s/mm2), which yielded a sensitivity of 94% (81–99% at 95% CI) and a specificity of 71% (44–90% at 95% CI). The AUC value was 0.89 at 95% CI (0.77–0.96) for differentiation between responders and non-responders.

The predictive of the pretreatment ADC value to distinguish responders tumors and non-responders to NCT has been evaluated in a number of studies. More than authors have shown that the pre-treatment ADC value was correlated with the response to the NCT . They showed prior NCT, mean ADC value of responders was lesser than in non-responders[16,17,25]. comparable findings were accounted by **Li et al.**[29], with a P value of (0.001). This result was also confirmed by other studies[27,30] . In the study **Iacconi et al.**[31], investigated the mean diffusivity (MD) in 21 women with LABC they disclosed that MD pretreatment of responders ($0.99\pm0.27\times 10^{-3}$ mm^2/s) was significantly (p=0.025) lower than MD pretreatment of non-responders ($1.46\pm0.33\times 10^{-3}$ mm^2/s). Also **An YY, et al.**[27] suggested that the best pretreatment cut-off for DWI to differentiate responders from non-responders was 0.59 (95% CI = 0.28 to 0.89) with 66.67 (9.43-99.16) sensitivity and 70.59 (44.04-89.69) specificity. In addition, observation by Wilmes, et al.[30] observation was that pretreatment tumor ADC metrics measured by HR-DWI (but not by STD-DWI) were generally lower for the responders than for the non-responders, they are in agree with other studies. Therefore, the significant alterations that occurred in ADC values pretreatment recommend that this parameter could be a suitable surrogate biomarker for assessing response to therapy in breast tumors.

There are three studies **Fangberget, et al.**[14], **Iwasa, et al.**[21] did not observe any correlation between pretreatment ADC and tumor response. **Belli et al.**[23] didn't noted a statistically significant difference in ADC value pretreatment between the responders versus the nonresponders. However, a significant inverse correlation among mean ADC value increase and therapy response was detected for responders. They also noted the cutoff for ADC value increase of >20% provided better diagnostic performance.

In studies that investigated early response monitoring, assessment with DWI observed a high significant change of ADC posttreatment in responders at early response monitoring, which was not observed in the non-responders group[16,18,25,29,32] this finding is in agreement with another study; **Shin, et al.[17]** showed Post-treatment ADC value in the group pCR was higher than that in the group non-pCR (1.47±0.24)× 10^{-3} mm^2/s versus (1.10±0.24)× 10^{-3} mm^2/s; (p=0.003) with ADC cut-off value to differentiate pCR from non-pCR was 1.19±10^{-3} mm^2/s, resulted in a sensitivity of 100% and a specificity of 70%.

Fangberget, *et al.*[14] noted that the non-pCR patients with a marked ADC increase (44%) were a near-pCR. Compared with baseline values, mean ADC significantly increased post treatment (1.4×10^{-3} mm^2/s, p<0.001). Furthermore, mean value of ADC in pCR group (1.7× 10^{-3} mm^2/s; range, 1.0–2.1×10^{-3} mm^2/s) was higher significantly than that of non-pCR group (1.2× 10^{-3} mm^2/s; range, 0.9–1.7×10^{-3} mm^2/s) (p=0.022), whereas ADC increase was not. They suggest using a cut-off of 1.42×10^{-3} mm^2/s to obtain high combined sensitivity (88%) and specificity (80%). **Belli, *et al.*[23]** . they observed a statistically significant inverse correlation between the percentage change of ADC and tumor regression grade (TRG class) (tau = -0.415, p < 0.001) with high sensitivity (80%), specificity (84%) and accuracy (82%). They also noted the cutoff for ADC value increase of >20% provided better diagnostic performance. This observation was also confirmed by extra studies[29-31]. **Pickles, *et al.*[33]**. observed the patients undergoing NACT, ADC values increased from baseline at the 1st cycle time point and only demonstrated a borderline significant difference among the pre-treatment and 2ed cycle time points (P=.057). In contrast, for the ADC results, significant differences were noted between the pre-treatment and 1st cycle (P=.005) time points and the pre-treatment and 2ed cycle time points (P=.004).

Most studies used dynamic contrast-enhanced MRI (DCE-MRI) and diffusion weighted imaging (DWI) in predicting treatment response in patient with LABC undergoing NAC. Two studies , **Park, et al.[24] and An YY, et al.[27]** attempted to compare the evaluation of NACT response using DWI and PET/CT, these studies showed not significant differences in specificity or accuracy were observed between the techniques (p>0.05). The agreement was reasonable between PET/CT and histology (κ=0.590), between DWI and histology (κ=0.494) and between DWI and PET/CT (κ=0.516) . In another study, **Shin, et al.[17]** used DWI and magnetic resonance spectroscopy for predicting pCR in patients exposed to NAC the results showed that MRS parameters and ADC post NAC were significantly different among the pCR and non-pCR groups. The percentage post-NACT changes in the absolute and normalized tCho integral in the group pCR were higher than in the non-responders (P = 0.020 and 0.023) but the change in tCho SNR was not significantly different among the two groups. more than, result that ADC was the only showing pre-treatment parameter a significant difference among pCR and groups non-pCR. The post-treatment ADC in the group pCR was significantly higher than that in the group non-pCR 1.43 × 10^{-3} mm2/s vs 1.10 × 10^{-3} mm2/s (P = 0.003). The percentage ADC value change inthe pCR group was higher than that in the non-pCR group (81.3% vs 12.6%; P < 0.001). They further recommended that optimal cut-off of the percentage ADC change for predicting group pCR was 40.7%, yielding 100% sensitivity and 91% specificity. And another study**, Iwasa, et al.[21]** used DWI and ultrasonography showed Ultrasonography reported to be useful in evaluating axillary lymph node metastases, intraductal cancer spread and outcomes of various conservative therapies for breast cancer.

Several studies demonstrated there was no significant difference in mean age between patients with pCR (44.4 years) and patients with residual tumors (42.3 years) (p=0.538)[17,24]. **Park, et al.[16]** showed there was no significant difference in mean age between responders (43.0 years) and non-responders (45.2 years) (P= .425).

In an attempt to evaluate the accuracy of the ADC value in predicting the response to NACT at baseline in patients according to their breast tumor, **Richard, *et al.*[28]** found there was no significant difference in the mean ADC measured before chemotherapy for all tumor type between pCR (1.055 ± 0.136× 10^{-3} mm^2/s) and non pCR (1.061 ± 0.222×10^{-3} mm^2/s; P=0.600). However, in the triple-negative subtype, the pretreatment mean ADC was significantly lower in pCR patients (1.060 ± 0.14310^{-3} mm^2/s) than in non pCR patients (1.227 ±0.271×10^{-3} mm^2/s, P=0.047). In this tumor subtype, the best pretreatment ADC cutoff value to detect non pCR was 1.291×10^{-3} mm^2/s, which yielded a sensitivity of 100 %, a specificity of 38 % and accuracy of 69%.

Their results also show that there are differences in the pretreatment mean ADC between the tumor subtypes. The mean ADC was significantly lower in the luminal A and luminal B subtypes than in the triple-negative subtype. However, in the luminal A and B subtypes, no significant differences exist in prechemotherapy ADC values between pCR and non-pCR cases.

Many conducted researches have revealed that DCE-MRI is capable to provide early responses to treatments in size or vascularity[25,33,34]. Thereafter, ADC exhibited noteworthy variation as early as subsequently the first cycle of therapy, whereas changes in the structural parameters, diameter and volume, were obvious only after the second cycle[16,25,33]. Other surveys could show that pretreatment ADC values and their early changes after treatment were related to changes in tumor volume after treatment[16,29,35]. **Sharma, et al.[25]** disclosed the average percentage reduction in tumor volume and diameter was not substantial between responders and non-responders. **Park, et al.[16]** observed no significant difference was between responders and

non-responders in terms of mean pretreatment tumor sizes (P=.537). Two different researches conducted via **Nilsen, *et al*.**[32] exhibited that enlarged ADC during NACT does not connect with tumor volume modifications. In addition, **Woodhams, *et al*.**[26] stated that the ADC previous to NACT did not associate with tumor size alteration (r = 0.110, *P* = 0.36) and did not support to discriminate PCR cases from patients with remaining ailment (*P* = 0.64). The variation in ADC from pre- to post-NACT did not link to the change measured size at contrast enhanced MRI (r = 0.175, *P* = 0.15) in the latter study.

IV. Discussion

The previous studies have showed the undertaking outcomes in utilizing DWI to predicted and evaluate response to NACT in breast cancer but consistency is not available. For that reason, we decided to afford a evocative systematic review of the experiential findings in the selected studies. The different results of many studies done in chemotherapy regimens (including more than five special regimens) plus the response criteria in imaging and pathological investigation not allowed us to employ statistical models in order to doing a meta-analysis. In case of study population, the patients showed a tumor 1.5 cm size or more. The TNM staging criteria was used to distinguish early breast tumor and locally advanced breast cancers.

The small tumor foci after NACT may be ignored in DWI owing to the limited spatial resolution. Additional work is required to conclude the most effectual post-therapy way for DWI evaluation. There is no agreement of the greatest b-value used in the aforementioned DWI studies (600–3000 s/mm2). For lesion conspicuity and finding purposes, a higher b value may be preferred. In a study by **Woodhams, *et al*.**[26] where they compared DWI acquired at b values of 1000 and 1500 s/mm2 in 120 patients, it was found that contrast ratio was significantly perfected at a higher b value, and that SNR and contrast to noise ratio were higher at 1000 s/mm2. Most standard DWI sequences use b = 0 s/ mm2 as the reference for calculating ADC, but nonzero b value reference images may be preferable in vivo to avoid perfusion and flow desecration. However, diagnostic advantage was not clearly shown in one study investigating this approach[36].

Here, we showed a multiplicity of concerns once confronting the most effective procedure for monitoring breast cancer response post-NACT treatments. Possibly the most significant issue is to homogenize the description and sorting of response to NACT. This was highlighted in the meta-analysis by **Marinovich, *et al*.**[37] in which the precision of MRI in sensing residual breast carcinoma after NACT differed as stated by different PCR descriptions. All the studies discussed above have been used in different criteria to outline tumor response either using evaluation on CE-MRI or existence of tumor on pathological specimens once definitive surgical treatment. Correspondingly, no consensus is gotten in the ideal b-values used in the DWI methods. All in all, further investigation is needed in breast NACT with large or multi-center studies via exact tumor response arrangement in which reflects PCR as it have proved before as a gold standard technique in PCR. The studies should comprise DWI with standardized practices used in order to establish whether there are cut-off values of ADC that could possibly be used to obviously foresee the responders against non-responders. Undoubtedly, quick detection is vital whenever you confronting patients who suffer from end stages of breast cancer. Variations in morphological factors including volume and diameter of tumor have been used with limited achievement, particularly for expecting early response.

Henceforward, there is need to decide a parameter based on biochemical or functional features of the tumor, or a grouping of parameters, which can be utilized to guess early tumor retort. Conducted researches have showed evaluations in structural factors (tumor volume and diameter) and the functional parameter (ADC) in patients with LABC. Measurements were done before NACT plus after I, II and III NACT via conventional MRI and DWI, and the potential of these parameters for observing tumor reaction was assessed. The sensitivity, specificity and accuracy of these factors in considering tumor response (individually and in combination) were dogged and linked to clinical response. Moreover, the role of ADC in distinguishing among response and non-response breast cancer was assessed[25].

Numerous fascinating annotations aroused from the study. The results signpost that the pre-therapy ADC of response was meaningfully lower than that of the non response[16,17,25,29]. Additionally, the average ADC of benign lesion was upper than that of the malignant tissue, demonstrating the potential of ADC to differentiate benign lesions from malignant ones[36]. Parallel findings were gotten from a study by **Woodhams, et al.**[26]. High cell increase in malignant tumors rises the cellular density, which declines the water fraction of the extracellular volume, in that way decreasing the ADC **Li, et al.**[29] exploring the role of DW-MRI ADC values in foretelling treatment response in patients with LABC experiencing NAC presented an inverse relation between ADC and tumor cellularity. The current results are in contract with aforementioned studies[16,17,25,26]. Several surveys also illustrated a momentous growth in the ADC of the tumor after I NACT compared with the pre-therapy value, and the modification was considerably different in clinical responders compared with non-responders. Nonetheless, the average percentage decreased after I NACT in volume and diameter wasn't significantly different among responders and non-responders. This prepossess the possible of the ADC to differentiate non-responders from responders at an early phase of management. Afterward II and III NACT, the

factors showed important differences in the changes between responders and non-responders. **Pickles, et al.[33]** have stated a similar comment.

The advanced growth in ADC and the lessening in tumor volume in responders are in agreement with the changes in the tumor physiology and morphology in response to therapy. The response to NCT varies among patients, which may be attributed to genetic variation, drug resistance, diet, etc. The increase ADC value after treatment may be due to cell damage mediated by the therapeutic interventions. Besides, the integrity of cell membranes is conceded, and the fractional volume of the interstitial space rises because of apoptosis or cell loss[38]. These changes are imitated as an increase in the movement of water in the damaged tissue. A decrease in cellularity of breast cancer tissue subsequently NACT compared with pre-therapy has also been recognized[39]. It has been stated that NACT upsurges apoptosis within 24 h after its start in breast cancer[40]. More confirmation of an escalation in ADC as the consequence of chemotherapy induced apoptosis comes from numerous clinical and pre-clinical studies[41].

We had several limitations as other studies done in this subject[42-44]. Primary, publication bias requests attention in systematic review wherever small studies with less promising results have a tendency to be less frequently published or never. Therefore, overestimation of current confident findings is potential. Following, the absence of consistency among revised studies banned us from executing a meta-analysis. For that reason, we selected to accomplish a systematic review of the selected studies and described observed findings as opposed to performing a meta-analysis that uses statistical assessments. Alterations in study purposes, chemotherapy regimens, response calculation criteria, patient sample size and breast cancer subtypes disallowed us from assuming more decisive conclusions. As the last point, the population size of the widely held studies is moderately insignificant. Merely five studies had a sample size beyond 50 subjects and the mainstream of the studies were one-center studies.

V. Conclusion

DWI has many advantages as a biomarker to predict and monitor NAC in LABC women as it provides early response indicators based on information on microstructural changes related to therapy effects with the passage of time that usually follow alterations in tumor size and the mean of apparent diffusion coefficient (ADC) respectively. Moreover, the indication on recognizing non-response earlier before treatment may encourage changing in therapeutic strategies to avoid toxicity, direct individualization of treatment and, consequently, enhance patients' outcome and increase overall survival. DWI is ionizing radiation free, not demand on injection of isotope or any other contrast medium. Likewise, the acquirement time of DWI is relatively short and its technique is straightforwardly repeatable to deliver assessable information. We recommend evaluating the different MR parameters with ADC value in order to see the accuracy of DWI assessment of responses to therapies. Similarly variation of course of therapy/treatment should be reported better described in development therapy and progression therapy response .To underpin promising results presented in this systematic review, further larger studies using standardized approaches are necessary to validate whether ADC can be used as a biomarker predictive for breast cancer therapy among LABC patients. Future studies should consider different cancer subtypes, tumor staging, chemotherapy protocols and imaging techniques to cover area of early evaluation of NACT, detection of return and estimate of long-term survival.

REFERENCES

[1]. Frederick L, Page DL, Fleming ID, Fritz AG, Balch CM, Haller DG, et al. AJCC cancer staging manual: Springer Science & Business Media; 2002.

[2]. Fisher B, Brown A, Mamounas E, Wieand S, Robidoux A, Margolese RG, et al. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. Journal of clinical oncology. 1997;15(7):2483-93.

[3]. Rastogi P, Anderson SJ, Bear HD, Geyer CE, Kahlenberg MS, Robidoux A, et al. Preoperative chemotherapy: updates of national surgical adjuvant breast and bowel project protocols B-18 and B-27. Journal of Clinical Oncology. 2008;26(5):778-85.

[4]. Londero V, Bazzocchi M, Del Frate C, Puglisi F, Di Loreto C, Francescutti G, et al. Locally advanced breast cancer: comparison of mammography, sonography and MR imaging in evaluation of residual disease in women receiving neoadjuvant chemotherapy. European radiology. 2004;14(8):1371-9.

[5]. Johansen R, Jensen LR, Rydland J, Goa PE, Kvistad KA, Bathen TF, et al. Predicting survival and early clinical response to primary chemotherapy for patients with locally advanced breast cancer using DCE- MRI. Journal of Magnetic Resonance Imaging. 2009;29(6):1300-7.

[6]. Heldahl MG, Lundgren S, Jensen LR, Gribbestad IS, Bathen TF. Monitoring neoadjuvant chemotherapy in breast cancer patients: improved MR assessment at 3 T? Journal of Magnetic Resonance Imaging. 2011;34(3):547-56.

[7]. Lobbes M, Prevos R, Smidt M. Response monitoring of breast cancer patients receiving neoadjuvant chemotherapy using breast MRI–a review of current knowledge. journal of cancer therapeutics and research. 2012;1(1):34.

[8]. Tozaki M, Oyama Y, Fukuma E. Preliminary study of early response to neoadjuvant chemotherapy after the first cycle in breast cancer: comparison of 1 H magnetic resonance spectroscopy with diffusion magnetic resonance imaging. Japanese journal of radiology. 2010;28(2):101-9.

[9]. Mulkern RV, Gudbjartsson H, Westin C-F, Zengingonul HP, Gartner W, Guttmann CR, et al. Multi-component apparent diffusion coefficients in human brain². NMR Biomed. 1999;12:51-62.

[10]. Niendorf T, Dijkhuizen RM, Norris DG, van Lookeren Campagne M, Nicolay K. Biexponential diffusion attenuation in various states of brain tissue: Implications for diffusion- weighted imaging. Magnetic Resonance in Medicine. 1996;36(6):847-57.

[11]. Mulkern RV, Zengingonul HP, Robertson RL, Bogner P, Zou KH, Gudbjartsson H, et al. Multi- component apparent diffusion coefficients in human brain: relationship to spin- lattice relaxation. Magnetic resonance in medicine. 2000;44(2):292-300.

[12]. Pilatus U, Shim H, Artemov D, Davis D, Van Zijl P, Glickson JD. Intracellular volume and apparent diffusion constants of perfused cancer cell cultures, as measured by NMR. Magnetic resonance in medicine. 1997;37(6):825-32.

[13]. Woodhams R, Ramadan S, Stanwell P, Sakamoto S, Hata H, Ozaki M, et al. Diffusion-weighted imaging of the breast: principles and clinical applications. Radiographics. 2011;31(4):1059-84.

[14]. Fangberget A, Nilsen L, Hole KH, Holmen M, Engebraaten O, Naume B, et al. Neoadjuvant chemotherapy in breast cancer-response evaluation and prediction of response to treatment using dynamic contrast-enhanced and diffusion-weighted MR imaging. European radiology. 2011;21(6):1188-99.

[15]. Murata Y, Kubota K, Hamada N, Miyatake K, Tadokoro M, Nakatani K, et al. Diffusion-weighted magnetic resonance imaging for assessment after neoadjuvant chemotherapy in breast cancer, based on morphological concepts. Oncology letters. 2010;1(2):293-8.

[16]. Park SH, Moon WK, Cho N, Song IC, Chang JM, Park I-A, et al. Diffusion-weighted MR imaging: pretreatment prediction of response to neoadjuvant chemotherapy in patients with breast cancer. Radiology. 2010;257(1):56-63.

[17]. Shin HJ, Baek HM, Ahn JH, Baek S, Kim H, Cha JH, et al. Prediction of pathologic response to neoadjuvant chemotherapy in patients with breast cancer using diffusion- weighted imaging and MRS. NMR in Biomedicine. 2012;25(12):1349-59.

[18]. Yankeelov TE, Lepage M, Chakravarthy A, Broome EE, Niermann KJ, Kelley MC, et al. Integration of quantitative DCE-MRI and ADC mapping to monitor treatment response in human breast cancer: initial results. Magnetic resonance imaging. 2007;25(1):1-13.

[19]. Partridge SC, McDonald ES. Diffusion weighted magnetic resonance imaging of the breast: protocol optimization, interpretation, and clinical applications. Magnetic resonance imaging clinics of North America. 2013;21(3):601-24.

[20]. Fattaneh A. Tavassoli PD. pathology and genetics of tumours of the breast and female genital organs. World Health Organization; 2003. 1-430 p.

[21]. Iwasa H, Kubota K, Hamada N, Nogami M, Nishioka A. Early prediction of response to neoadjuvant chemotherapy in patients with breast cancer using diffusion-weighted imaging and gray-scale ultrasonography. Oncology reports. 2014;31(4):1555-60.

[22]. Kawamura M, Satake H, Ishigaki S, Nishio A, Sawaki M, Naganawa S. Early prediction of response to neoadjuvant chemotherapy for locally advanced breast cancer using MRI. Nagoya journal of medical science. 2011;73(3-4):147.

[23]. Belli P, Costantini M, Ierardi C, Bufi E, Amato D, Mule A, et al. Diffusion- weighted Imaging in Evaluating the Response to Neoadjuvant Breast Cancer Treatment. The breast journal. 2011;17(6):610-9.

[24]. Park SH, Moon WK, Cho N, Chang JM, Im S-A, Park IA, et al. Comparison of diffusion-weighted MR imaging and FDG PET/CT to predict pathological complete response to neoadjuvant chemotherapy in patients with breast cancer. European radiology. 2012;22(1):18-25.

[25]. Sharma U, Danishad KKA, Seenu V, Jagannathan NR. Longitudinal study of the assessment by MRI and diffusion- weighted imaging of tumor response in patients with locally advanced breast cancer undergoing neoadjuvant chemotherapy. NMR in Biomedicine. 2009;22(1):104-13.

[26]. Woodhams R, Kakita S, Hata H, Iwabuchi K, Kuranami M, Gautam S, et al. Identification of residual breast carcinoma following neoadjuvant chemotherapy: diffusion-weighted imaging—comparison with contrast-enhanced MR imaging and pathologic findings. Radiology. 2010;254(2):357-66.

[27]. An YY, Kim SH, Kang BJ, Lee AW. Treatment response evaluation of breast cancer after neoadjuvant chemotherapy and usefulness of the imaging parameters of MRI and PET/CT. Journal of Korean medical science. 2015;30(6):808-15.

[28]. Richard R, Thomassin I, Chapellier M, Scemama A, de Cremoux P, Varna M, et al. Diffusion-weighted MRI in pretreatment prediction of response to neoadjuvant chemotherapy in patients with breast cancer. European radiology. 2013;23(9):2420.

[29]. Li X-r, Cheng L-q, Liu M, Zhang Y-j, Wang J-d, Zhang A-l, et al. DW-MRI ADC values can predict treatment response in patients with locally advanced breast cancer undergoing neoadjuvant chemotherapy. Medical oncology. 2012;29(2):425-31.

[30]. Wilmes LJ, McLaughlin RL, Newitt DC, Singer L, Sinha SP, Proctor E, et al. High-resolution diffusion-weighted imaging for monitoring breast cancer treatment response. Academic radiology. 2013;20(5):581-9.

[31]. Iacconi C, Giannelli M, Marini C, Cilotti A, Moretti M, Viacava P, et al. The role of mean diffusivity (MD) as a predictive index of the response to chemotherapy in locally advanced breast cancer: a preliminary study. European radiology. 2010;20(2):303-8.

[32]. Nilsen L, Fangberget A, Geier O, Olsen DR, Seierstad T. Diffusion-weighted magnetic resonance imaging for pretreatment prediction and monitoring of treatment response of patients with locally advanced breast cancer undergoing neoadjuvant chemotherapy. Acta oncologica. 2010;49(3):354-60.

[33]. Pickles MD, Gibbs P, Lowry M, Turnbull LW. Diffusion changes precede size reduction in neoadjuvant treatment of breast cancer. Magnetic resonance imaging. 2006;24(7):843-7.

[34]. Theilmann RJ, Borders R, Trouard TP, Xia G, Outwater E, Ranger-Moore J, et al. Changes in water mobility measured by diffusion MRI predict response of metastatic breast cancer to chemotherapy. Neoplasia. 2004;6(6):831-7.

[35]. Jensen LR, Garzon B, Heldahl MG, Bathen TF, Lundgren S, Gribbestad IS. Diffusion- weighted and dynamic contrast- enhanced MRI in evaluation of early treatment effects during neoadjuvant chemotherapy in breast cancer patients. Journal of Magnetic Resonance Imaging. 2011;34(5):1099-109.

[36]. Peters NH, Vincken KL, van den Bosch MA, Luijten PR, Mali WPTM, Bartels LW. Quantitative diffusion weighted imaging for differentiation of benign and malignant breast lesions: The influence of the choice of b- values. Journal of Magnetic Resonance Imaging. 2010;31(5):1100-5.

[37]. Marinovich ML, Houssami N, Macaskill P, Sardanelli F, Irwig L, Mamounas EP, et al. Meta-analysis of magnetic resonance imaging in detecting residual breast cancer after neoadjuvant therapy. Journal of the National Cancer Institute. 2013;105(5):321-33.

[38]. Galons J-P, Altbach MI, Paine-Murrieta GD, Taylor CW, Gillies RJ. Early increases in breast tumor xenograft water mobility in response to paclitaxel therapy detected by non-invasive diffusion magnetic resonance imaging. Neoplasia. 1999;1(2):113-7.

[39]. Rajan R, Poniecka A, Smith TL, Yang Y, Frye D, Pusztai L, et al. Change in tumor cellularity of breast carcinoma after neoadjuvant chemotherapy as a variable in the pathologic assessment of response. Cancer. 2004;100(7):1365-73.

[40]. Archer C, Parton M, Smith I, Ellis P, Salter J, Ashley S, et al. Early changes in apoptosis and proliferation following primary chemotherapy for breast cancer. British journal of cancer. 2003;89(6):1035-41.

[41]. Woodhams R, Matsunaga K, Iwabuchi K, Kan S, Hata H, Kuranami M, et al. Diffusion-weighted imaging of malignant breast tumors: the usefulness of apparent diffusion coefficient (ADC) value and ADC map for the detection of malignant breast tumors and evaluation of cancer extension. Journal of computer assisted tomography. 2005;29(5):644-9.

[42]. Chen J-H, Su M-Y. Clinical application of magnetic resonance imaging in management of breast cancer patients receiving neoadjuvant chemotherapy. BioMed research international. 2013;2013.

[43]. Lobbes M, Prevos R, Smidt M, Tjan-Heijnen V, Van Goethem M, Schipper R, et al. The role of magnetic resonance imaging in assessing residual disease and pathologic complete response in breast cancer patients receiving neoadjuvant chemotherapy: a systematic review. Insights into imaging. 2013;4(2):163.
[44]. Prevos R, Smidt M, Tjan-Heijnen VC, van Goethem M, Beets-Tan R, Wildberger J, et al. Pre-treatment differences and early response monitoring of neoadjuvant chemotherapy in breast cancer patients using magnetic resonance imaging: a systematic review. European radiology. 2012:1-10.

*Vahid Changizi. "Diffusion-Weighted MRI in Monitoring Locally Advance Breast Cancer Response to Neoadjuvant Chemotherapy." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) , vol. 16, no. 08, 2017, pp. 95–104.