



Assessment of Tumor Response to Neoadjuvant Chemotherapy in Breast Cancer Using MRI and ¹⁸F-FDG PET/CT

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ABSTRACT

Objective: Neoadjuvant chemotherapy (NACT) has been the primary treatment method for patients with local advanced breast cancer. A pathological complete response (pCR) to therapy correlates with better overall disease prognosis. Magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET/CT) have been widely used to monitor the response to NACT in breast cancer. The aim of this study was to assess tumor response to NACT by MRI and PET/CT, to determine which imaging modality is more accurate in detecting tumor response post NACT in breast cancer.

Materials and Methods: A retrospective review of our database revealed 34 women with breast cancer that had MRI and PET/CT performed prior to and after NACT, followed by definitive surgery. For response assessment, we calculated the difference in maximum diameter of the tumor in MRI and difference in standard uptake values in PET/CT. The correspondence rate between the imaging modalities and pCR were calculated. For the prediction of pCR, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were analyzed.

Results: The assessment of tumor response to NACT showed 11 cases with pCR (32%), 15 pathological partial response (44%) and eight pathological no response (24%). The correspondence rate between MRI and pathological response was 50% (17/34), compared to 65% (22/34) for PET/CT. For prediction of pCR, MRI showed higher specificity compared to PET/CT (78.2% vs. 73.9%, $p = 0.024$), while the accuracy of PET/CT was significantly higher (79.4% vs. 70.5%, $p = 0.004$). PET/CT also had a higher NPV compared to MRI (94.4% vs. 78.2%, $p = 0.002$). There were no differences in terms of sensitivity and PPV between MRI and PET/CT.

Conclusion: Compared to MRI, PET/CT was more likely to correlate with the pathological response after NACT. For the prediction of pCR, PET/CT proved to be a more accurate imaging modality to monitor response after NACT than MRI.

Keywords: Breast cancer, MRI; neoadjuvant chemotherapy; pathological response; PET/CT

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Key Points

- The aim of neoadjuvant chemotherapy (NACT) is to achieve pCR, which correlates well with the overall prognosis.
- Magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET/CT) are increasingly used to monitor the tumor response after NACT, with certain limitations.
- There are no recommendations as to which imaging modality is the gold standard for assessing tumor response after NACT.
- This study showed that while PET/CT was more accurate than MRI for predicting pCR, combined use of both imaging modalities optimizes prediction of residual disease.

Introduction

Neoadjuvant chemotherapy (NACT) has been widely accepted as the primary treatment method for patients with locally advanced and inoperable breast cancer (1). Additional recommendations include its use in triple-negative or human epidermal growth factor receptor 2 (HER2) -positive breast cancers that are node-positive and/or larger than 2 cm, as it influences adjuvant therapy decisions in these patients

(2). Moreover, NACT allows time to delay surgery, while waiting for genetic testing results or considering reconstructive options (3). The aim of NACT is to downstage tumors and to de-escalate the extent of surgical treatment, facilitating breast conserving surgery (BCS) and less aggressive axillary surgery (4). Having a pathological complete response (pCR) following NACT correlates with better overall prognosis, with an improved five-year survival rate of 89% reported in those receiving NACT compared to those not achieving pCR (5).

Accurately identifying tumor response to therapy can only be made after final histological examination following definitive surgery (4). This leads to a delay in identifying the response to NACT during the course of treatment, either by excessive or deficient combination therapy, or by exposing patients to a prolonged treatment course with unwanted chemotherapy effects and might even result in incomplete or more aggressive surgery. Therefore, in order to evaluate the tumor response earlier during the course of neoadjuvant therapy and prior to definitive surgery, it is necessary to determine which imaging modality is more accurate (4, 5).

Tumor response has been traditionally evaluated by clinical examination, mammogram and ultrasound, with difficulty in differentiating fibrosis from residual tumor, limiting their efficacy (5, 6). Magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET/CT) have been increasingly used to monitor response to NACT in breast cancer. They assess the morphological characteristic and the tumor function, respectively (6). There are many studies exploring the ideal imaging modality to evaluate the tumor response to NACT, but no consensus has been reached (5, 7). Moreover, the majority of the studies in literature evaluated MRI and PET/CT separately, in different cohorts of patients. Therefore, the aim of the present study was to assess the tumor response to NACT using both imaging modalities in the same group of patients with breast cancer, keeping pCR as the reference standard, in order to determine whether MRI or PET/CT was more accurate in detecting tumor response post NACT in breast cancer.

Materials and Methods

The study was approved by the Research Ethics Committee of the Government Hospitals in Bahrain (approval number: 65-230524, date: 23.05.2024). A retrospective review of our database revealed 209 female patients with biopsy-proven breast cancer who underwent NACT from January 2018 to December 2022. Patients were included if they had MRI and PET/CT performed prior to and after NACT, followed by definitive surgery. Patients who did not have both imaging modalities and those with missing data were excluded. Only 34 patients met the inclusion criteria and were analyzed.

The following data were collected from the patients' medical records: age at diagnosis; tumor type; tumor size; tumor grade; oestrogen receptor; progesterone receptor and HER2 status; Ki-67 index; clinical stage; NACT regimen and cycles; type of surgery; and final histopathological stage.

In order to evaluate tumor response in MRI, the maximum diameter of the tumor (Dmax) before and after chemotherapy were recorded. For assessment of tumor response in PET/CT, the tumor maximum standardized uptake value (SUV) before and after chemotherapy were recorded. The pathological response to chemotherapy was kept as the reference standard. Absence of invasive tumor was considered as pCR, however, ductal carcinoma *in situ* (DCIS) may be present. A change in the stage of the tumor following NACT was considered a pathological partial response (pPR). Tumors that did not show pCR or pPR were considered as pathological non-responder tumors (pNR). A radiological complete response (rCR) in MRI was absence of tumor enhancement in imaging after chemotherapy. A radiological partial response (rPR) was at least a 30% reduction in the Dmax of the tumour following therapy and the others were considered as radiological no response (rNR). In PET/CT, absence of fluorine-18

fluorodeoxyglucose (¹⁸F-FDG) uptake was considered as rCR. A reduction of at least 50% in SUV was considered as rPR and all others were considered as rNR.

Statistical Analysis

Changes in the Dmax were calculated using the following equation: $[(Dmax_pre - Dmax_post)/Dmax_pre] \times 100$, where Dmax_pre was the maximum tumor diameter in pre-chemotherapy MRI and Dmax_post was post-chemotherapy. Changes in SUV were calculated as: $[(SUVpre - SUVpost)/SUVpre] \times 100$, where SUVpre and SUVpost were the maximum SUV uptake in PET/CT pre- and post-chemotherapy, respectively. The correspondence rates of tumor response between both imaging modalities and the final histopathological diagnosis were calculated. Demographic data were analyzed using means and percentages. To predict pCR, we compared the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy between both imaging modalities using the McNemar test. Statistical analysis were performed using Statistical Package for the Social Sciences software, version 29.0 (IBM Inc., Chicago, IL, USA) and $p < 0.05$ values were considered to be significant.

Results

The mean age of the patients was 46 years (range 33-66 years). The clinical stages of the patients at the time of presentation were: stage I in one patient (2.9%); IIA in 10 patients (29.4%); IIB in 10 patients (29.4%); IIIA in seven patients (20.6%); IIIB in four patients (11.8%); and IIIC in two patients (5.9%). Most (91.2%) had invasive ductal carcinoma. The NACT regimen was determined by tumor biology and the clinical stage. Of the 34 patients, 58.8% of patients were HER2-positive and therefore received six cycles of a combination of docetaxel, carboplatin, trastuzumab and pertuzumab. The remaining 14 patients received four cycles of doxorubicin, cyclophosphamide and paclitaxel. Chemotherapy was started within two weeks following initial imaging. The mean time interval between completion of chemotherapy and breast MRI was 17 days. The mean time interval between completion of chemotherapy and PET/CT was 18 days. The mean time interval between breast MRI and PET/CT after chemotherapy was 5 days. All patients underwent surgery approximately six weeks following NACT. Types of surgical procedure were: modified radical mastectomy n=13; mastectomy with sentinel lymph node biopsy (SLNB) n=7; BCS and axillary clearance n=5; and BCS with SLNB n=9.

Furthermore, the mean tumor size on pre-chemotherapy MRI was 5.75 cm (range 1.3–16 cm), with mean reduction in Dmax following treatment of 63%, ranging from 11% to complete reduction. One patient showed 87% increase in size following chemotherapy, indicating disease progression. The mean tumor SUV in the pre-chemotherapy PET/CT was 12.3 (range 2.8–30.8), with the mean reduction in SUV following treatment was 85.4% (range 3–100% reduction).

The histopathological characteristics and tumor response following NACT are shown in Table 1. Of the 34 patients, 23 (68%) had residual invasive tumor seen on final histopathology. The pathological tumor responses were as follows: 11 pCR (32%), 15 pPR (44%) and 8 pNR (24%). The correspondence rate between MRI and pathological response was 50% (17/34), compared to 65% (22/34) between PET/CT and pathological response, as shown in Table 2. MRI correctly assessed 6 of the 11 pCR (54.5%) cases, whereas PET/CT accurately assessed 10 of the 11 patients with pCR (90.9%). One pCR case was

Table 1. Histopathological characteristics and tumor response following neoadjuvant chemotherapy

Pathological complete response (n=11)		Pathological partial response (n=15)		Pathological no response (n=8)	
Age		Age		Age	
48 (35-62)		45 (33-55)		47 (33-66)	
Histological subtype		Histological subtype		Histological subtype	
IDC	10	IDC	13	IDC	8
ILC	1	ILC	0	ILC	0
MC	0	MC	2	MC	0
Tumor grade		Tumor grade		Tumor grade	
Grade 1	1	Grade 1	0	Grade 1	0
Grade 2	7	Grade 2	4	Grade 2	8
Grade 3	3	Grade 3	11	Grade 3	0
ER status		ER status		ER status	
Positive	8	Positive	9	Positive	7
Negative	3	Negative	6	Negative	1
PR status		PR status		PR status	
Positive	8	Positive	8	Positive	6
Negative	3	Negative	7	Negative	2
HER2 status		HER2 status		HER2 status	
Positive	8	Positive	8	Positive	4
Negative	3	Negative	7	Negative	4
Ki-67 index		Ki-67 index		Ki-67 index	
<20%	3	<20%	2	<20%	1
>20%	8	>20%	13	>20%	7
MRI response		MRI response		MRI response	
CR	6	CR	4	CR	1
PR	5	PR	9	PR	5
NR	0	NR	2	NR	2
PET/CT response		PET/CT response		PET/CT response	
CR	10	CR	3	CR	3
PR	1	PR	11	PR	4
NR	0	NR	1	NR	1

ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; MC: Mucinous carcinoma; CR: Complete response; PR: Partial response; NR: No response; MRI: Magnetic resonance imaging; PET/CT: Positron emission tomography/computed tomography

Table 2. Correlation of pathological tumor response with response in MRI and PET/CT

		MRI			PET/CT			
		Patients	rCR	rPR	rNR	rCR	rPR	rNR
Pathological response	pCR	11	6	5	0	10	1	0
	pPR	15	4	9	2	3	11	1
	pNR	8	1	5	2	3	4	1
	Total	34	11	19	4	16	16	2

pCR: Pathological complete response; pPR: Pathological partial response; pNR: Pathological no response; rCR: Radiological complete response; rPR: Radiological partial response; rNR: Radiological no response; MRI: Magnetic resonance imaging; PET/CT: Positron emission tomography/computed tomography

assessed as rPR in PET/CT, which correlates with the residual DCIS seen on histopathology. For the 15 pPR cases, the correspondence rate of MRI was 60% (9/15) and PET/CT 73% (11/15). For the 8 cases of pNR, the correspondence rate of MRI was 25% (2/8) and PET/CT was 12.5% (1/8).

Prediction of the pCR by PET/CT and MRI is shown in Table 3. While PET/CT showed a higher sensitivity (90.9% *vs.* 54.5%) and PPV (62.5% *vs.* 54.5%) compared to MRI, this was not significantly better ($p = 0.130$ and $p = 0.722$, respectively). The specificity of MRI was significantly higher than PET/CT (78.2% *vs.* 73.9%, $p = 0.024$). PET/CT showed a significantly greater NPV (94.4% *vs.* 78.2%, $p = 0.002$) and accuracy (79.4% *vs.* 70.5%, $p = 0.004$) in predicting pCR than MRI.

Discussion and Conclusion

In recent years, NACT has been an essential aspect of the treatment plan for locally advanced and inoperable breast cancers, in order to provide patients with the possibility of BCS, and to increase the rate of negative margins in the final histopathological specimen (1, 2). The ultimate aim of NACT is to achieve pCR, which correlates positively with the patient prognosis (4, 8).

In order to assess tumor response to NACT in breast cancer during therapy or prior to surgery and for early identification of non-responders, so as to switch to different regimens, many imaging modalities have been used, with certain advantages and limitations (5, 6). Currently, there are no established guidelines as to which modality is the gold standard to evaluate tumor response (7). The National Comprehensive Cancer Network (NCCN) guidelines recommend physical examination and repeating the initial imaging modality that detected an abnormality in the staging process (9). Traditionally, physical examination and conventional imaging modalities, such as mammogram and ultrasound, have been used, with a reported accuracy of 57%, 74% and 79%, respectively. Physical examination may be limited, where, in a palpable lesion, it is not possible to differentiate fibrosis from residual disease and the absence of a palpable lesion does not confirm CR (10). Mammogram is more sensitive than physical examination to detect residual disease, but the presence of architectural distortion and microcalcifications may underestimate the treatment response (11).

Breast MRI has been widely used to evaluate the local extent of the primary disease, multicentricity, bilaterality and to differentiate scarred tissue from local recurrence in patients who previously underwent BCS (12). MRI, done before and after therapy, is an optional recommendation in the NCCN guidelines (13). MRI is

superior to ultrasound and mammogram in evaluating response to NACT (14). Contrast enhanced MRI is based on neo-angiogenesis. Tumors have more blood vessels and higher permeability compared to normal cells and so have increased contrast uptake. An enhancing lesion correlates with a viable tumor. Tumor necrosis due to therapy results in inflammation and formation of granulation tissue, which enhances in MRI, resulting in overestimation of the tumor size. Also, certain chemotherapeutic agents have anti-angiogenic effects without necrosis, resulting in lack of enhancement and underestimation, thereby limiting its accuracy (12).

Furthermore, PET/CT can be used in staging and re-staging of stage III, locally advanced, inflammatory, recurrent or metastatic breast cancer, or if there are suspicious results in conventional staging investigations, as per the recent NCCN guidelines (9, 15). ¹⁸F-FDG is a glucose analogue, and undergoes the same initial pathway of glucose metabolism, but due to the lack of a hydroxyl group, it does not get metabolized further and gets trapped in the cell. Malignant cells have higher glucose metabolism, resulting in an increased uptake and entrapment of ¹⁸F-FDG, increasing their detection through PET/CT scan. Nevertheless, increased glucose metabolism is seen physiologically; in the brain and muscles, and in inflammatory and infectious processes, limiting its specificity (15). Many published studies and meta-analyses were done to evaluate the superiority of either MRI or PET/CT in assessing the tumor response to therapy, with variable results (5, 7).

NACT usually starts two to four weeks after diagnosis and completion of initial staging imaging, while surgery should not be delayed beyond eight weeks following last chemotherapy cycle for accurate assessment of tumor response. For an effective correlation between MRI and PET/CT, it is recommended that the time interval between the two modalities must not exceed two weeks (1, 6), as in our study. In order to evaluate the radiological response to treatment, the pathological response has been used as a reference standard in all previous studies so the same criterion was applied in our study.

The rCR rate assessed by MRI was 32.4% (11/34) and PET/CT was 47% (16/34), with similar results reported in literature (6). In addition, the rate of false rCR by MRI was higher compared to that by PET/CT in our study. One reason for this discrepancy is that, MRI interpretation is limited by fibrosis and scar formation, resulting in higher false positive results (12). For the prediction of pCR after NACT, several studies have concluded that PET/CT was superior to MRI, showing similar results to our study (16-18). However, two studies reported that the performance of MRI was similar to PET/CT (7, 19). Therefore, the combined use of these two imaging modalities may increase the possibility to evaluate pCR accurately. PET/MRI is a

Table 3. Prediction of the pCR by MRI and PET/CT

Parameter	MRI	PET/CT	p-value
Sensitivity %	54.5 (6/11)	90.9 (10/11)	0.130
Specificity %	78.2 (18/23)	73.9 (17/23)	0.024
Positive predictive value %	54.5 (6/11)	62.5 (10/16)	0.772
Negative predictive value %	78.2 (18/23)	94.4 (17/18)	0.002
Accuracy	70.5 (24/34)	79.4 (27/34)	0.004

pCR: Pathological complete response; MRI: Magnetic resonance imaging; PET/CT: Positron emission tomography/computed tomography

new imaging modality that was first introduced in 2010. It combines the advantages of both PET and MRI, by assessing the metabolic activity of the tumor and its vascularity, with higher contrast resolution compared to PET/CT (9, 20). Studies showed that the addition of MRI to PET scans significantly improves its sensitivity and specificity, which opens an area for future research (21, 22).

Limitations of our study include its retrospective nature and single-center experience. Although our sample size was relatively small, this is probably because not all of our patients who underwent NACT had the indications for both MRI and PET/CT to be performed. Furthermore, our study focused on the tumor response to therapy without evaluating axillary lymph node involvement, which could be explored in a future study.

In conclusion, this study demonstrated that, after NACT for breast cancer, the use of PET/CT had a better correlation with the pathological response than MRI in terms of assessing the tumor response. For the prediction of pCR, PET/CT was a more accurate method, while MRI was a more specific imaging modality. The complementary value of combined use of both imaging modalities is perhaps the most important way to improve diagnostic performance in the setting of NACT. Nevertheless, further larger prospective studies, including randomized controlled trials, are needed to evaluate other methods, which should include PET/MRI.

Ethics

Ethics Committee Approval: The study was approved by the Research Ethics Committee of the Government Hospitals in Bahrain (approval number: 65-230524, date: 23.05.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: R.Y.A-B., F.Y.B., H.A.A.; Concept: R.Y.A-B., F.Y.B., H.A.A.; Design: R.Y.A-B., F.Y.B., H.A.A.; Data Collection and/ or Processing: R.Y.A-B., F.Y.B.; Analysis and/or Interpretation: R.Y.A-B., H.A.A.; Literature Search: R.Y.A-B., F.Y.B.; Writing: R.Y.A-B., F.Y.B., H.A.A.

Conflict of Interest: The authors have no conflicts of interest to declare.

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