ejpmr, 2021,8(12), 50-54

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

PET/CT IS MORE HELPFUL THAN CONVENTIONAL TECHNIQUES IN REVEALING METASTASES OF BREAST CANCER

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Article Received on 09/10/2021 **Article Revised on 30/10/2021** **Article Accepted on 19/11/2021**

ABSTRACT

Background: Breast cancer with extensive tumours have a risk of 8.3-15.1% for metastasis. Positron emission tomography/computed tomography (PET/CT) can precisely reveal metastases during staging of breast cancer. **Aim:** To compare the sensitivity and specificity of PET/CT versus conventional techniques for revealing metastases in breast cancer. **Methods:** Our prospective and double-blind investigation included 167 subjects with breast cancer, aged 49.6 years (31-75) at King Hussein hospital, KHMC, Amman, Jordan, during the period 2010-2020. For stage II or III breast cancer, CXR, scintigraphy and CT of the abdomen were used. For stage IV breast cancer, CXR, scintigraphy, CT of the abdomen and PET/CT were used. PET/CT when conventional techniques were unclear and for staging of inflammatory breast cancer. PET/CT was compared with conventional techniques. Sensitivity and specificity in revealing metastases were recorded for PET/CT and conventional techniques. Metastases were recorded according to consecutive MRI, ultrasound or plain radiography. If there were no metastases, follow-up was done for 24 months. Fisher's exact test was used to assess differences in sensitivity and specificity between PET/CT and conventional techniques. **Results:** 58 subjects had metastases according to pathological (20), radiological (22) or clinical (16) criteria. Of the 109 subjects with no metastases, 15 subjects relapsed and 94 subjects were disease-free. The locations of relapse in these 15 subjects were the local lymph nodes (3), distant lymph nodes (2), bone (2), brain (3), lung (3) and liver (2). Regarding the conventional techniques, 86 subjects (51.5%) had doubtful metastases and 50 (58.1%) of 86 subjects were positive for metastases. Metastases by location were in the bone (48), thoracic lymph nodes (18), lung (7) and liver (13). The sensitivity and specificity of PET/CT in revealing metastases were 91.9% and 85.7%, respectively, and those of conventional techniques were 80.4% and 61.8%, respectively. The sensitivity and specificity of PET/CT were remarkably higher than conventional techniques ($P < 0.005$, for both). Eight subjects with metastases revealed by PET/CT were clinically occult and metastases had not been revealed by conventional techniques. **Conclusion:** PT/CT has better sensitivity and specificity than conventional techniques in revealing metastases of breast cancer.

KEYWORDS: PET/CT; conventional techniques; breast cancer; metastases; sensitivity; specificity.

INTRODUCTION

For some frequent cancers, therapy for spreading pathology is non-curative, expensive and toxic. Management to lengthen life span with tumour shrinkage of 10-15% is used nowadays. Due to reduced reaction incidence in cancer, radiology has a role in continuing, modifying or stopping therapy. Radiology has a role also in choosing which new protocols should be adopted. Cure is often attained in hematologic cancers and rarely in disseminated solid cancers.

Breast cancer with extensive tumours have a metastasis risk of 8.3-15.1%.[1,2] For staging of locally advanced breast cancer, it is recommended to use chest radiography, mammogram and breast ultrasound. Others are indicated by the clinical picture, such as breast magnetic resonance; scintigraphy; computed tomography (CT), ultrasound or MRI of the abdomen; CT, ultrasound, or MRI of the pelvis; and positron emission tomography (PET)/CT.[3] Conventional techniques have limitations regarding the accurate observation of breast cancer metastases.[4]

Whole-body PET has been used in breast cancer staging.[5] In breast cancer, PET reveals recurrences for a precise recording of the spread of the disease.[6] Conventional techniques with PET can reveal unanticipated metastases on staging.[5] PET in women with breast cancer is still questionable.[1] PET/CT is more sensitive than conventional techniques in revealing metastases of breast cancer.[7-9]

The goal of this investigation was to compare the sensitivity and specificity of PET/CT versus

conventional techniques, i.e. CT, ultrasound, radiography and scintigraphy, in revealing breast cancer metastases.

METHODS

This prospective and double blind investigation included 167 subjects with breast cancer, aged 49.6 years (31-75) at King Hussein hospital, KHMC, Amman, Jordan, during the period 2010-2020, after obtaining approval from our local ethical and research board review committee at the Jordanian Royal Medical Services. For staging of breast cancer, PET/CT was compared with conventional techniques. Sensitivity and specificity in revealing metastases were recorded for PET/CT and conventional techniques. Subjects with chemotherapy or endocrine therapy pre-PET/CT were excluded (Table I).

For stage II or III breast cancer, CXR, scintigraphy and CT of the abdomen were used. For stage IV breast cancer, CXR, scintigraphy, CT of the abdomen and PET/CT were used. PET/CT is indicated for unclear results after using conventional techniques and for the staging of inflammatory breast cancer (Table II).

For the delivery of ^{18}F-FDG-PET/CT, an intravenous administration of 555-740 MBq (15-20 mCi) of ^{18}F-FDG was performed, and 1-1.5 h later,2-3 scans were achieved at 3- to 5-minute intervals. Non-contrast CT was used at 120 kV, 300 mA, 0.5-second rotation from the base of the skull to the mid-thigh at a 3.75-mm slice thickness. Conventional techniques included CXR, scintigraphy and CT of the chest, abdomen, or pelvis with intravenous contrast.

Metastases were recorded according to pathological results or consecutive MRI, ultrasound or plain radiography. If there were no metastases, follow-up was done for 24 months. Doubtful metastases were diagnosed as tumour continuation by conventional techniques, PET/CT or MRI. A positive metastasis was recorded if a metastasis was doubted or there was an indeterminate pathology. Positive for benign disease was recorded if there was no metastasis or the pathology was benign. Response Evaluation Criteria in Solid Tumours for solid lesions on conventional imaging[10], PET Response Criteria in Solid Tumours for PET/CT[11] and the MD Anderson criteria for bone lesions[12] were used to determine interval changes.

Statistics

Sensitivity and specificity were measured according to the number of subjects. Fisher's exact test was used for the discrepancies in sensitivity and specificity precision between PET/CT and conventional techniques. A p-value less than 0.05 was considered statistically significant.

RESULTS

The indications for PET/CT were: doubtful on conventional imaging (84), locally advanced breast cancer (70), excluded primary cancer (7), idiopathic (3) and subject demand (3). In total, 58 subjects had metastases according to pathological (20), radiological (22) or clinical (16) criteria. One hundred and nine subjects had no metastases, of whom 42 were firstly assessed for metastases by PET/CT only (4), conventional techniques (37) or PET/CT and conventional techniques (1). The same 42 subjects had no metastases according to pathological (6), radiological (23) or clinical (13) criteria. Of the 109 subjects with no metastases, 15 subjects relapsed and 94 subjects remained disease-free. The locations of relapse in these 15 subjects were local lymph nodes (3), distant lymph nodes (2), bone (2), brain (3), lung (3) and liver (2).

Regarding the conventional techniques; 86 subjects (51.5%) had doubtful metastases and 50 (58.1%) of 86 subjects were positive for metastases. The sensitivity of conventional techniques in revealing metastases was 80.4% and the specificity was 61.8% (Table III). Regarding PET/CT, 103 subjects had no doubtful metastases. Three of 103 subjects had metastases, one by biopsy and the other two by radiological methods. The sensitivity of PET/CT in revealing metastases was 91.9%. According to PET/CT, 66 subjects had doubtful metastases. Ten of these 66 subjects did not have metastases by biopsy (1), radiological methods (6) or clinical criteria (8). The specificity of PET/CT in revealing metastases was 85.7%.

The sensitivity of PET/CT (91.9%) was remarkably greater than the sensitivity of conventional techniques (80.4%) ($P < 0.005$). The specificity of PET/CT (85.7%) was remarkably greater than the specificity of conventional techniques (61.8%) ($P < 0.005$). In 11 subjects, PET/CT indicated metastases not indicated by conventional techniques. In 8 of 11 subjects, metastases were diagnosed by biopsy or conventional techniques (Table IV). In the other three subjects, metastases were not diagnosed by biopsy or conventional techniques.

Altogether, 42 subjects had bone metastases. PET/CT revealed bone metastases in 40, failed to reveal bone metastases in 2 and incorrectly indicated bone metastases in 4 subjects. Scintigraphy revealed bone metastases in 23, failed to reveal bone metastases in 8 and incorrectly indicated bone metastases in 14 subjects. The sensitivity and specificity of PET/CT for revealing bone metastases were 92.5% and 90.5%, respectively, compared with 70.5% and 80.5%, respectively, for scintigraphy (Table V). 18 subjects had metastases in the lymph nodes of the chest and 10 subjects had lung metastases. PET/CT revealed three mediastinal nodal metastases and two hilar nodal metastases not revealed by chest CT. Sixteen subjects had liver metastases. Both PET/CT and abdominal CT precisely revealed liver metastases in all these patients. PET/CT incorrectly showed liver metastases in 2 subjects and abdominal CT incorrectly showed liver metastases in 7 subjects. In revealing liver metastases, the sensitivity and specificity of PET/CT were 94.5% and 93.5%, respectively, compared with 94.5% and 89.5%, respectively, for CT.

Of 167 subjects, 109 were negative for metastases and 58 subjects were positive for metastases. Of 109 subjects, 15 subjects had a relapse and 94 had no relapse. Of 58 subjects, 43 had diagnosed metastases, of whom 20 were diagnosed by pathology and 23 were diagnosed by radiology. Of 58 subjects, 15 subjects had no diagnosed metastases. The location of 86 metastases was in the bone (48), thoracic lymph nodes (18), lung (7) and liver (13).

Table IL Study group features.

Feature	**No(%)**
NO	167
Sex F	167
Average age (years), range	49.6 (31-75)
Primary cancer	
T0/N1, 2, 3	4, 1, 1
T1/N0, 1, 3	15, 5, 3
T2/N0, 1, 2, 3	14, 16, 1, 12
T3/N0, 1, 3	3, 6, 4
T4 a-c/N0, 1, 2, 3	3, 2, 3, 14
T4d/N0, 1, 2, 3	3, 13, 4, 40
TOTAL	167

Table II. Study group cancer features.

Feature		**No(%)**
Staging	**I**	14(8.4)
	II	30(17.96)
	III a	4(2.4)
	III b	21(12.6)
	III c	40(23.95)
	IV	58(34.7)
TOTAL		167
METASTASES	**M0**	109(65.3)
	M1	58(34.7)
TOTAL		167
Nuclear grade	**I**	4(2.4)
	II	50(29.9)
	III	107(64.1)
	idiopathic	6(3.6)
TOTAL		167

Table III. Features of conventional techniques.

Technique			
	Yes(no)	**No(no)**	**Doubted metastases(no)**
CXR	167	0	11
Scintigraphy	150	17	45
Chest CT	84	83	30
Abdominal CT	143	24	41
Abdominal ultrasound	8	159	2
Pelvic CT	37	130	12

Table IV: Sensitivity and specificity.

	metastases by PET/CT			**metastases by conventional techniques**		
	positive	**negative**	**overall**	**positive**	**negative**	**overall**
Metastases						
Positive	56	2	58	38	20	58
Negative	10	99	109	48	61	109
Overall		101		86	81	
Sensitivity	66	91.9%	167		80.4%	167
Specificity		85.7%			61.8%	

Table V. Metastases revealed by PET/CT but not by conventional techniques.

1	Conventional	Metastasis location	Metastasis no.
1	CXR, BUS, MMG, BMRI, SS, CCT	bone	2
2	CXR, BUS, MMG, BMRI, SS, CCT, ACT, PCT	bone	1
3	CXR, BUS, MMG, BMRI	bone	>2
4	CXR, BUS, MMG, SS, CCT, ACT, PCT	LN (hilar)	1
5	CXR, BUS, MMG, SS, CCT, ACT,	bone	>2
6	CXR, BUS, MMG, SS, CCT, ACT,	LN (mediastinal)	1
7	CXR, BUS, MMG, SS	Bone, LN, lung	>2
8	CXR, BUS, MMG, ACT, AUS	LN (neck), bone	>2

ACT: abdominal CT; BMRI: breast MRI; BUS: breast ultrasonography; CCT: chest CT; MMG: mammography; PCT: pelvic CT.

DISCUSSION

FDG-PET is a prototypical molecular radiological method. FDG is a structural glucose analogue labelled with the positron emitter fluorine-18. Substitution of fluorine for a hydroxyl group blocks the metabolism of the tracer. The FDG uptake reflects the rate of trapping of phosphorylated FDG and is an indication of the rate of glycolysis. Malignant cells consume more glucose, with increased accumulation of fluorodeoxyglucose. In 2000, integrated PET/CT was able to provide functional and anatomical data.

We tried to our best to evaluate the use of PET/CT for revealing metastases in staging of breast cancer. Seventy-eight (35%) subjects had metastases at initial staging. PET/CT had higher sensitivity and specificity than conventional techniques. PET/CT revealed metastases not recorded on conventional techniques in 11 (14%) of the 78 subjects. Precise observation of metastases is crucial. In a metastasis, operative excision of the breast tumour may not be recommended. If bone metastases are revealed, they can be managed. Solitary metastases can be managed with mixed methods.

PET/CT is more precise than conventional techniques for revealing of metastases.[7,9,13] PET or PET/CT could be more handful than scintigraphy for revealing of bone metastases.[14] PET/CT was more important than scintigraphy in revealing bone metastases. PET/CT might substitute scintigraphy as the primary method for revealing of bone metastases in the staging of recently confirmed breast cancer. FDG-PET might reveal metastases in breast cancer with increased precision to substitute conventional techniques.[15] For 15 subjects in this investigation, systemic treatment was modified according to PET/CT imaging indicating stage IV disease. In 11 of these 15 subjects, metastases were diagnosed, but not in the other 4 patients. The systemic treatment for stage IV disease in those 4 subjects may not have been required.

Quantitative ^{18}F-FDG PET was started for the early follow-up of tumour reaction of breast cancer in 1993, to rapidly evaluate if a tumour is reacting to treatment. Primarily, women with recently confirmed breast cancer had a fast and remarkable reduction in the influx percentage of ^{18}F-FDG 8 days after beginning therapy. Quantitative non-anatomic radiological techniques are used as biomarkers of cancer reaction to anticipate the efficiency of therapy. PET with ^{18}F-FDG is one of the strongest biomarkers. PET nowadays is used in the confirmation, staging, restaging and management follow-up of many cancers. Qualitative ^{18}F-FDG PET imaging at the end of therapy have been integrated into the lymphoma reaction evaluation in the IWC + PET criteria. Not all of our subjects had complete assessments with conventional techniques, reducing the efficiency of conventional techniques for revealing metastases. Pathologic results were not recorded for all regions of doubtful metastases, as biopsy was avoided in cases with multiple doubtful metastases and when results were indicative of metastatic disease so therapy could be directed to progressive disease. Few subjects with doubtful distant metastases with biopsy had a benign biopsy, meaning that a biopsy must be done to diagnose doubtful metastasis.

CONCLUSION

PET/CT is more important than conventional techniques according to the sensitivity and specificity of revealing metastases of breast cancer and should be used in the assessment of metastatic disease in breast cancer.

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