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Comparing Local Recurrence and Distant Metastasis Between Breast-Conserving Therapy with Radiotherapy and Total Mastectomy in Candidates for PET/CT Assessment

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ABSTRACT

Background: This study aimed to compare the recurrence rate of breast cancer between women treated with breast-conserving therapy (BCT) with/without radiotherapy and those treated with total mastectomy using 18F-fluorodeoxyglucose positron emission tomography/computed tomography¹⁸ (F-FDG PET/CT).

Methods: The current study retrospectively included 588 patients suffering from breast cancer who had been referred to the PET/CT department of Masih-e-Daneshvari Hospital in Tehran between April 2013 and September 2019. Data of all female patients with breast cancer were extracted from the recorded hospital files. Based on the treatment plan, patients were divided into two groups: BCT with/without radiotherapy (n=168) and total mastectomy (n=420). Local, locoregional, and distant metabolically active lesions were determined in¹⁸ F-FDG PET/CT and compared between groups.

Results: BCT and total mastectomy were comparable regarding local (28.5% vs. 25.7%, P=0.200) and locoregional (21.4% vs. 22.8%, P=0.712) recurrence, while distant recurrence was significantly higher with total mastectomy (88.5% vs. 64.2%, P<0.001). Also, lymph node invasion (42.9% vs. 60%^m P<0.001) and positive PET/CT (78.5% vs. 88.5%, P=0.002) were significantly higher with total mastectomy.

According to multivariate analysis, age, clinical stage, and positive margin are independently correlated with the rate of distant metastasis.

Conclusion: According to our analysis, breast-conserving therapy could be a suitable choice of surgery in selected patients since local and locoregional recurrence rate did not significantly differ between patients who underwent breast-conserving surgery compared to those who were treated with total mastectomy. Higher rate of distant metastasis in patients with total mastectomy seems to be influenced by many confounding variables such as age, higher stage of diagnosis and positive margin rather than type of surgery.

Introduction

Breast cancer is the most common diagnosed cancer and the most common cause of death from cancer in women.¹ Breast cancer treatment is either local (surgical and radiotherapy) or systemic (chemotherapy, hormonal or biological therapy). The treatment plan is determined based on multiple prognostic factors including tumor histology, clinical and pathologic features of the primary

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tumor, axillary lymph node involvement, presence of hormone receptors (ER/PR/ HER2), genetic predisposition, age, comorbidities, and distant metastases.² Patients' preference plays a key role in decision making, especially when the existing therapies are not superior to one another. The results of clinical trials in the past two decades have shown that type of surgical procedures in the early stages of breast cancer do not have a significant impact on the survival of patients; therefore, the conservative surgical method has become widespread and is broadly accepted among patients. Death from breast cancer usually occurs following a relapse, which is even possible in the early stages of cancer when the tumor is small and there is no regional lymph node involvement.³ Approximately 70% of recurrences occur within the first three years with maximal incidence within one or two years of diagnosis.⁴ Recent studies have demonstrated that the frequency of recurrence in patients treated conservatively is higher than those undergoing total mastectomy. Furthermore, the interval between surgery and the first recurrence is associated with distant recurrence and therefore has a prognostic value.⁵ Studies have shown that the survival of patients who experience local recurrence within five years of surgery is significantly lower than those who develop local recurrence after five years.⁶ Given the development of diagnostic methods, as well as treatment based on tumor biology (hormone receptor status, genetic mutations, etc.), recurrence rates after different surgical approaches need to be investigated and compared. The purpose of this study was to evaluate breast cancer recurrence rates based on ¹⁸F-FDG PET/CT findings in women treated with BCT (with/without radiotherapy) and total mastectomy. The practical aim of this study was to improve the stratification of patients and to select the optimal surgical procedure in patients with breast cancer.

Methods

Study population and data extraction

The present study was a cross-sectional study to determine and compare the frequency of recurrence in patients treated with breast-conserving therapy with/without radiotherapy and total mastectomy based on ¹⁸F-FDG PET/CT findings. In this regard, 588 consecutive patients suffering from breast cancer referred to the PET/CT department of Masih-e-Daneshvari Hospital in Tehran between April 2013 and September 2019 were assessed. Data of all female patients with breast cancer were extracted from the recorded hospital files. Based on the treatment plan, patients were divided into two groups: BCT with/without radiotherapy (n=168) and total mastectomy (n=420). Patients with a history of breastfeeding, recent breast manipulation, as well as patients referred for staging were excluded. Then, by reviewing the picture archiving and communication system (PACS), ¹⁸F-FDG PET/CT images of the

remaining patients were retrieved and the presence of local recurrence (metabolically active lesions in breast tissue or site of the previous surgery between the skin and chest wall), locoregional recurrence (presence of metabolically active lymphadenopathy in ipsilateral axillary, infraclavicular, supraclavicular, internal mammary lymph nodes), and the presence and number of distant recurrences by viscera and location of lymph nodes (metabolically active lesions in distant viscera or lymph nodes) were determined by a nuclear medicine physician and a radiologist side by side and in consensus.

¹⁸F-FDG PET/CT protocol

¹⁸F-FDG PET/CT imaging were performed on all patients using the following protocol: with 2.1 MBq/kg ¹⁸F-FDG injections after at least 6-hour fasting and observing a 24-hour carbohydrate-free diet containing protein and fat and resting in a supine position with minimal light and sound for an hour. One hour after the injection, patients underwent ¹⁸F-FDG PET/CT using a PET/CT scanner (TOF, Discovery 690 GE). First, craniocaudal CT images were obtained using the following parameters: auto mAs (adults: 50-120), 120 kV, noise factor 19, 2.5 mm thickness. Immediately after CT imaging, craniocaudal PET imaging was performed. The time for each bed position was three minutes and the imaging field was vertex to mid-thigh. At the end of the imaging, PET images were iteratively reconstructed using HD technique.

PET/CT interpretation

Images of all selected patients were retrieved from PACS. PET (AC and non-AC) and CT images in all three axial, coronal, and sagittal sections were reviewed using the AW VolumeShare 4.5 software by a team consisting of a radiologist and a nuclear medicine specialist. Local, locoregional, and distant metabolically active lesions were categorized qualitatively as definitely positive (moderate to severe uptake, higher than liver with or without the corresponding anatomy), probably positive (uptake similar to or slightly higher than liver with or without the corresponding anatomy), and equivocal (uptake lower than liver and higher than the background) or semi-quantitatively based on the SUVmax index. SUVmax measurement was semi-automatically done using the VolumeShare AW 4.5 software PET disc scanner (GE discovery 690) by inserting a spherical contour around the lesion at the point where maximal absorption was visualized. Imaging findings were recorded based on location and the number of lesions. Frequency, location, and number of tumor recurrences were compared between the two groups.

Statistical analysis

For statistical analysis, results were presented as mean \pm standard deviation (SD) for quantitative variables and were summarized by frequency



(percentage) for qualitative variables. Quantitative variables were compared using the Student's t-test or the Mann-Whitney test based on the normality of data distribution by the Kolmogorov-Smirnov test. Qualitative variables were, on the other hand, compared using the chi-square test. P values ≤ 0.05 were considered statistically significant. For statistical analysis, the Statistical Package for the Social Sciences (SPSS) software (version 25.0, Armonk, NY: IBM Corp.) was used.

Results

In total, 168 patients underwent BCT and 420 underwent total mastectomy. Comparison of baseline characteristics between the two groups (Table 1) showed a significantly higher mean age ($P=0.001$) but lower breast cancer-related genetic mutations in the BCT group compared to the total mastectomy group.

There was also a significant difference regarding the TNM classification as well as tumor staging between the two groups (Table 1). With regard to the tumor receptor status, ER positivity was revealed in 71.4% of the BCT group and 51.4% of the mastectomy group ($P<0.001$), PR positivity in 71.4% and 51.4% ($P<0.001$), HER2 positivity in 35.7% and 65.7% ($P<0.001$), and triple negative in 21.4% and 14.2% ($P=0.030$), respectively. In the PET/CT report, positive scans were found in 78.5% of patients in the BCT group and 88.5% of patients in the total mastectomy group ($P=0.002$). Regarding recurrence following intervention, there was no difference between the two groups with regard to local recurrence ($P=0.200$) and locoregional recurrence ($P=0.712$), while distant recurrence was significantly higher in the total mastectomy group compared to patients in the BCT group (88.5% vs. 64.2%, $P<0.001$) (Table 2).

Table 1. Baseline characteristics in the two intervention groups

Variables	Total	BCS+/-radiation (n=168, 28.6%)	Total mastectomy (n=420, 71.4%)	P
Age	51.6 \pm 11.8 (32-79)	54.35 \pm 13.8 (34-79)	50.51 \pm 10.77 (32-78)	0.001
<40	108 (18.4%)	24 (22.2%)	84 (77.8%)	0.12
≥ 40	480 (81.6%)	144 (30%)	336 (70%)	
Genetic mutation (of 576 tested)	420 (72.9%)	96 (22.9%)	324 (77.1%)	0.000
Clinical stage				0.000
I	60	60 (100%)	0	
II	300	96 (32%)	204 (68%)	
IIIA	228	12 (5.3%)	216 (94.7%)	
T				0.000
T1	216 (36.7%)	132 (61.1%)	84 (38.9%)	
T2	312 (53.1%)	24 (7.7%)	288 (92.3%)	
T3	60 (10.2%)	12 (20%)	84 (80%)	
N				0.000
N0	96 (16.3%)	24 (25%)	72 (75%)	
N1	276 (65.7%)	144 (34.3%)	132 (55%)	
N2	132 (24.4%)	0	132 (100%)	
N3	84 (14.3%)	0	84 (100%)	
Histopathology				0.000
IDC	336 (57.1%)	96 (28.6%)	240 (71.4%)	
ILC	168 (28.6%)	36 (21.4%)	132 (78.6%)	
Medullary	72 (12.2%)	36 (50%)	36 (50%)	
Others	12 (2%)	0	12 (100%)	
Highest tumor grade				
x	12 (2%)	0	12 (100%)	
I	96 (16.3%)	72 (75%)	24 (25%)	
II	348 (59.2%)	84 (24.1%)	264 (75.9%)	
III	132 (22.4%)	12 (9.1%)	120 (90.9%)	
Receptor status				
ER+	336 (57.1%)	120 (35.7%)	216 (64.3%)	0.000
PR+	336 (57.1%)	120 (35.7%)	216 (64.3%)	0.000
HER2+	336 (57.1%)	60 (17.9%)	276 (82.1%)	0.000
Triple negative	96 (16.3%)	36 (37.5%)	60 (62.5%)	0.03
Positive Margin	432 (73.5%)	144 (33.3%)	288 (66.7%)	0.000
Positive lymphovascular invasion	324 (55.1%)	72 (22.2%)	252 (77.8%)	0.000

Table 2. PET/CT findings and recurrence rates in the two intervention groups

Variables	Total	BCS	Total mastectomy	P
PET/CT findings				0.002
Positive scan	504 (85.7%)	132 (26.2%)	372 (73.8%)	
Negative scan	84 (14.3%)	36 (42.9%)	48 (57.1%)	
Local recurrence				0.2
Yes	156 (28.9%)	48 (30.8%)	108 (69.2%)	
No	384 (71.1%)	96 (25%)	288 (75%)	
Locoregional recurrence				0.7
Yes	132 (23.9%)	36 (27.3%)	96 (72.7%)	
No	420 (76.1%)	108 (25.7%)	312 (74.3%)	
Distant metastasis				0.000
Yes	480 (87%)	108 (22.5%)	372 (77.5%)	
No	72 (13%)	36 (50%)	36 (50%)	

**Table 3.** Baseline characteristics in the two groups with positive and negative findings on PET/CT

Variables		PET/CT negative	PET/CT positive	P
Age		50 ±13.5 (35-78)	51.9±11.5 (32-79)	NS
Age	<40	24 (22.2%)	84 (77.8%)	0.009
	≥40	60 (12.5%)	420 (87.5%)	
Genetic mutation (of 576 tested)	YES	48 (11.4%)	372 (88.6%)	0.000
	NO	24 (15.4%)	132 (84.6%)	
Clinical T stage	IA	0	24 (100%)	0.000
	IB	12 (33.3%)	24 (66.7%)	
	IIA	24 (11.1%)	192 (88.9%)	
	IIB	24 (28.6%)	60 (71.4%)	
	IIIA	0	108 (100%)	
	IIIB	0	36 (100%)	
	IIIC	24 (28.6%)	60 (71.4%)	
T stage	T1	36 (16.7%)	180 (83.3%)	NS
	T2	36 (11.5%)	276 (88.5%)	
	T3	12 (20%)	48 (80%)	
N staging	N0	0	96 (100%)	0.000
	N1mi	12 (33.3%)	24 (66.7%)	
	N1	48 (20%)	192 (80%)	
	N2	0	132 (100%)	
	N3	24 (28.6%)	60 (71.4%)	
Histopathology	IDC	24 (7.1%)	312 (92.9%)	0.000
	ILC	36 (21.4%)	132 (78.6%)	
	medullary	24 (33.3%)	48 (66.7%)	
	others	0	12 (100%)	
Highest tumor grade	x	0	12 (100%)	0.003
	I	24 (25%)	72 (75%)	
	II	48 (13.8%)	300 (86.2%)	
	III	12 (9.1%)	120 (90.9%)	
Receptor status	ER+	36 (10.7%)	300 (89.3%)	0.004
	PR+	36 (10.7%)	300 (89.3%)	0.004
	HER2+	48 (14.3%)	288 (85.7%)	NS
	Triple negative	24 (25%)	72 (75%)	0.001
Margin	Negative	36 (8.3%)	396 (91.7%)	0.000
	Positive	48 (30.8%)	108 (69.2%)	
LV invasion	LVI +	36 (11.1%)	288 (88.9%)	0.01
	LVI -	48 (18.2%)	216 (81.8%)	
Type of surgery	BCS	36 (21.4%)	132 (78.6%)	0.002
	Total	48 (11.4%)	372 (88.6%)	

Comparison of baseline variables (Table 3) showed that except for age, tumor staging, and status of HER2 receptor, there was a significant difference between the groups with respect to other variables.

According to multivariate analysis, age, clinical stage, and positive margin are independently correlated with the rate of distant metastasis.

Discussion

The initial management of breast cancer has considerably changed within the recent decade which has influenced the incidence of local, regional, and even distant recurrences. Advancement in new therapeutic approaches such as partial mastectomy followed by radiotherapy has led to lower distant metastases as well as better long-term survival.⁷ In other words, BCT consisting of breast-conserving surgery (BCS) followed by radiation therapy has led to a considerable reduction in recurrence compared to routine total mastectomy regardless of baseline

characteristics such as tumor grading and staging as well as the presence of specific hormonal receptors.⁸ Overall, the long-term locoregional recurrence after concurrent BCS and radiotherapy has notably decreased in recent years.⁹ However, it has been shown that individuals who undergo BCS alone without radiation have generally higher local recurrence rates compared with those who also receive radiotherapy.^{10,11} In this regard, the findings of the present study with respect to lower distant metastasis following BCT compared to total mastectomy are predictable.

Some large population-based studies have compared the effectiveness of BCT and total mastectomy. Contrary to our findings, Van der Sangen et al.¹² showed that for a median follow-up of 7.4 years, the local recurrence risk for total mastectomy patients was 4.4%, while in the BCT cohort, the 5-year local recurrence risk was 8.3%, indicating a significant difference. In a study by



Mahmood et al.¹³, within a median follow-up of 5.7 years, no difference was found in the 5-, 10-, and 15-year rates of cause-specific survival between the two groups receiving total mastectomy or BCT. Subset analyses confirmed that there were no differences in outcomes for local treatment when stratified by age quartiles. Data from the literature, including randomized trials, have shown that locoregional recurrence occurs at a rate of 5% to 15% after conservative surgery or mastectomy plus adjuvant radiotherapy.¹⁴⁻¹⁸ The 10-year recurrence rate after conservative treatment was about 10% to 20% in patients with early stages of invasive breast cancer.¹⁹ The median time to recurrence, after the end of systemic adjuvant treatment, may be short (2–4 years) or significantly prolonged (5–8 years).¹⁹⁻²¹ However, many recent publications have shown that these delays may depend on prognostic factors, tumor biology, and molecular subtypes. Thus, the difference in the rates of local, locoregional or distant metastasis in both interventional approaches (conservative treatment or total mastectomy) may be correlated with several factors, especially biological behaviors of the tumor and histological features.

The higher rate of distant metastasis in patients with total mastectomy seems to be influenced by many confounding variables such as age, higher stage of diagnosis and positive surgical margin rather than the type of surgery.

In the current study, Radiotherapy was used for all patients undergoing breast-conservative surgery as a major complementary treatment and had an important role in local control of disease since there was no significant difference in local recurrence between the two groups.

There are major drawbacks in the current study. Regarding the retrospective nature of the study, patients' population may not potentially be a real representative of breast cancer patients and hence the results may be validated with caution.

According to our analysis, breast-conserving therapy could be a suitable choice of surgery in selected patients since local and locoregional recurrence rate did not significantly differ between patients who underwent breast-conserving surgery compared to those who were treated with total mastectomy. The higher rate of distant metastasis in patients with total mastectomy seems to be influenced by many confounding variables such as age, higher stage of diagnosis and positive margin rather than the type of surgery.

Conflict of Interest

None.

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