Three Nuclear Medicine diagnostic procedures and breast cancer mortality in women. A population-analysis in Taiwan based upon National Health Insurance database

Mao-Chin Hung[1] PhD,
Yu-Yi Huang[2] MD

1. Department of Medical Imaging and Radiological Sciences, Tzu Chi University of Science and Technology, Hualien, Taiwan.
2. Department of Nuclear Medicine, Koo-Foundation, Sun Yat-Sen Cancer Center, Taipei, Taiwan.

Keywords: Breast cancer
- NHIRD
- Whole-body bone scan
- Lymphoscintigraphy
- ^{18}F-FDG PET/CT

Corresponding author:
Mao-Chin Hung PhD
Department of Medical Imaging and Radiological Sciences,
Tzu Chi University of Science and Technology. 880, Sec. 2, Chien-Kuo Rd., Hualien, Taiwan.
Tel: 886-3-8572158#2436;
Fax: 886-3-8561396;
art@tcust.edu.tw

Received:
28 March 2019
Accepted revised:
14 June 2019

Abstract

Objectives: To investigate the correlation between the utilization of nuclear medicine diagnostic procedures and the mortality of women with breast cancer. **Subjects and Methods:** Based on the National Health Insurance Research Database (NHIRD), we studied female breast cancer patients in 2012 who underwent whole-body bone scan, lymphoscintigraphy, or fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) for possibly managing breast cancer metastases. The mortality of breast cancer was then followed up in 2017. Multiple linear regression analysis was applied to analyze the correlation between the use of any of these three nuclear medicine procedures and the mortality of breast cancer. **Results:** For patients with early-stage breast cancer, single lymphoscintigraphy was the most frequently performed nuclear medicine procedure, accounting for 36.4% of all three nuclear medicine procedures. For patients with late-stagebreast cancer, single whole-body bone scan was the most frequently performed nuclear medicine procedure, accounting for 67.2% of all three nuclear medicine procedures. Mortality of breast cancer significantly increased with the prevalence of late-stage breast cancer (b=2.87, P=0.001) and significantly decreased in cases in which whole-body bone scan was used (b=−4.28, P=0.003). **Conclusion:** The mortality of women with late-stage breast cancer was negatively related to the utilization of whole-body bone scan but not to the utilization of lymphoscintigraphy or the ^{18}F-FDG PET/CT scan. In women with early-stage breast cancer, no significant correlation existed between breast cancer mortality and the utilization of the above three nuclear medicine procedures.

Hell J Nucl Med 2019; 22(2): 111-115 *Epub ahead of print: 7 July 2019* *Published online: 20 July 2019*

Introduction

According to a 2018 estimation by the World Health Organization, the worldwide incidence of breast cancer was 1,671,149 (43.1 per 100,000 women), and the mortality was 521,907 (12.9 per 100,000 women) [1]. Moreover, the female breast cancer (464,000 cases) was the commonest cancer site and the third commonest cause of all deaths from cancer in Europe (131,000 cases) [2]. Therefore, diagnosing and controlling the incidence of metastases and reducing mortality in breast cancer women is critical.

Treatment modalities and survival of breast cancer depend among other factors, on the stage of cancer and the molecular aggressiveness of cancer cells. Nuclear medicine modalities contributing to the diagnosis of the stage of breast cancer include lymphoscintigraphy, which is used both to map the distribution of sentinel lymph nodes (SLN) which is needed for SLN biopsy and to identify the regional lymph nodes status [3, 4]. Furthermore, whole-body bone scan and fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) are used to identify metastases [5-7]. Nuclear medicine procedures have contributed to staging breast cancer, but the correlation between using the above three nuclear medicine procedures and the mortality of early-stage or late-stage breast cancer in women has not been studied.

The National Health Insurance (NHI) program was launched in Taiwan in 1995. The NHI is a mandatory single-payer health care system with a nearly 100% coverage rate and includes most nuclear medicine procedures such as lymphoscintigraphy, bone scan and ^{18}F-FDG PET/CT scan for a total of 77 items. All medical records, including types of nuclear medicine procedure, patients' age at examination, and clinical indications, are incorporated into the National Health Insurance Research Database (NHIRD). Based on the NHIRD, this study was conducted to investigate the correlation between the utilization of the above three nuclear medicine procedures and the mortality of women with breast cancer.

Table 1. *The prevalence and mortality of breast cancer in Taiwan.*

Age group in 2012	Early-stage breast cancer, 2012		Late-stage breast cancer, 2012		Age group in 2017	Death from breast cancer, 2017	
	Number	Prevalence*	Number	Prevalence*		Number	Mortality*
15~19	3	0.4	0	0.0	20~24	1	0.1
20~24	4	0.5	3	0.4	25~29	3	0.4
25~29	53	6.4	18	2.2	30~34	35	4.0
30~34	172	16.8	76	7.4	35~39	60	5.8
35~39	399	42.2	171	18.1	40~44	125	13.3
40~44	696	75.3	344	37.2	45~49	225	24.5
45~49	1,144	121.7	604	64.3	50~54	326	34.7
50~54	1,078	116.4	664	71.7	55~59	400	44.2
55~59	916	110.0	662	79.5	60~64	363	44.9
60~64	767	116.2	552	83.7	65~69	250	40.8
65~69	411	105.2	334	85.5	70~74	160	44.2
70~74	278	75.6	300	81.6	75~79	162	49.6
75~79	158	56.3	196	69.9	80~84	119	52.9
80~84	84	43.9	100	52.3	85~89	92	70.8
85~89	36	35.9	41	40.9	-	-	-
Total	6,199	61.9	4,065	40.6	Total	2,321	24.1

**per 100,000 women according to NHIRD*

Subjects and Methods

Subjects selection

According to the International Classification of Diseases, Ninth Revision, we selected and studied women with breast cancer from the NHIRD in 2012, having performed whole-body bone scans, lymphoscintigraphs, or ^{18}F-FDG PET/CT. The overall mortality of these women was followed-up in 2017. Because the mortality of breast cancer was associated with the staging of the disease and with age [8], patients were stratified by age and by the kind of surgical operation. Partial mastectomy patients were considered to be at an early stage and mastectomy patients at a late stage.

Statistical analysis

Descriptive statistics were adopted to analyze the utility and age distribution of the three nuclear medicine procedures in these patients. Multiple linear regression analysis with stepwise regression method was applied to analyze which nuclear medicine procedure(s)significantly affected the mortality of these patients. All statistical analyses were performed using IBM SPSS Statistics 19.0 (IBM Taiwan Corp., Taipei, Taiwan).

Results

In 2012, the total number of women older than 15 years in Taiwan was 10,010,348; the total number of partial mastectomies (early-stage breast cancer) was 6,199 (i.e., 61.9 per 100,000 women). The prevalence in various age groups was between 0.4 and 121.7 per 100,000; the highest in the 45-49 age group and the lowest in the 15-19 age group (Table 1). Furthermore in 2012, the total number of mastectomies (late-stage breast cancer) was 4,065 (i.e., 40.6 per 100,000 women). The prevalence was between 0.4 and 85.5 per 100,000; highest in the 65-69 age group and lowest in the 15-19 age group. Moreover, the total number of deaths from breast cancer was 2,321 in 2017 (i.e., 24.1 per 100,000 women). The mortality was between 0.3 and 57.6 per 100,000; it was highest in the 80-84 age group and lowest in the 15-19 age group.

The applications of single or multiple nuclear medicine procedures in managing breast cancer are shown in Table 2. We analyzed the use of nuclear medicine procedures in women with early-stage and with late-stage breast cancer in Taiwan, 2012. For patients with early-stage breast cancer, single lymphoscintigraphy was the most frequently performed nuclear medicine procedure, accounting for 36.4% of all three nuclear medicine procedures. For patients with late-stage breast cancer, single whole-body bone scan was the most usually performed test accounting for 67.2% of all three nuclear medicine procedures.

The utilization of nuclear medicine procedures differed among age groups; it was highest in the 45-49 age group of early-stage breast cancer, highest in the 60-64 age group of late-stage breast cancer and lowest in the 15-19 age group of all cases (Figures 1 to 4). The age of patients with late-stage breast cancer who used the three nuclear medicine procedures was higher than that of patients with early-stage breast cancer.

Table 2. *The use of nuclear medicine procedures in women with early-stage and with late-stage breast cancer in Taiwan, 2012.*

Nuclear medicine procedures	Use rate*	Distribution (%)
Women with early-stage breast cancer		
Single lymphoscintigraphy	15.8	36.4
Single whole-body bone scan	13.5	31.1
Whole-body bone scan & lymphoscintigraphy	11.3	26.0
Whole-body bone scan & ^{18}F-FDG PET/CT	1.1	2.5
Single ^{18}F-FDG PET/CT	0.9	2.1
Lymphoscintigraphy & ^{18}F-FDG PET/CT	0.5	1.2
Whole-body bone scan & lymphoscintigraphy & ^{18}F-FDG PET/CT	0.3	0.7
Total	43.4	100.0
Women with late-stage breast cancer		
Single whole-body bone scan	17.6	67.2
Whole-body bone scan & lymphoscintigraphy	3.3	12.6
Single lymphoscintigraphy	2.2	8.4
Single ^{18}F-FDG PET/CT	1.5	5.7
Whole-body bone scan & ^{18}F-FDG PET/CT	1.3	5.0
Lymphoscintigraphy & ^{18}F-FDG PET/CT	0.2	0.8
Whole-body bone scan & lymphoscintigraphy & ^{18}F-FDG PET/CT	0.1	0.4
Total	26.2	100.0%

per 100,000 women according to NHIRD

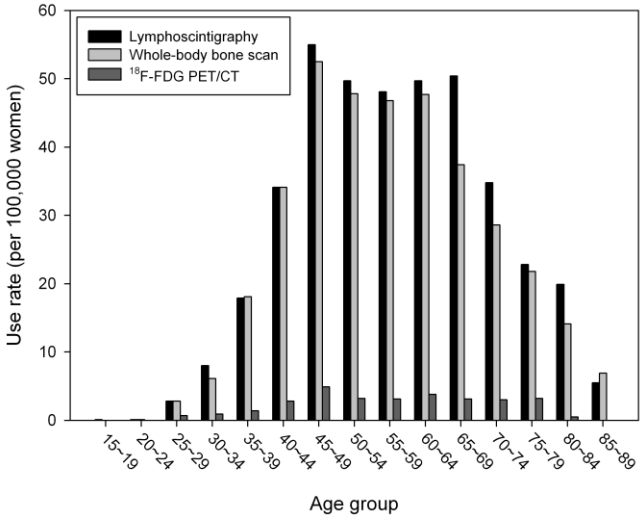

Figure 1. The age distribution of each of the three nuclear medicine procedures in patients with early-stage breast cancer in Taiwan, 2012 according to NHIRD.

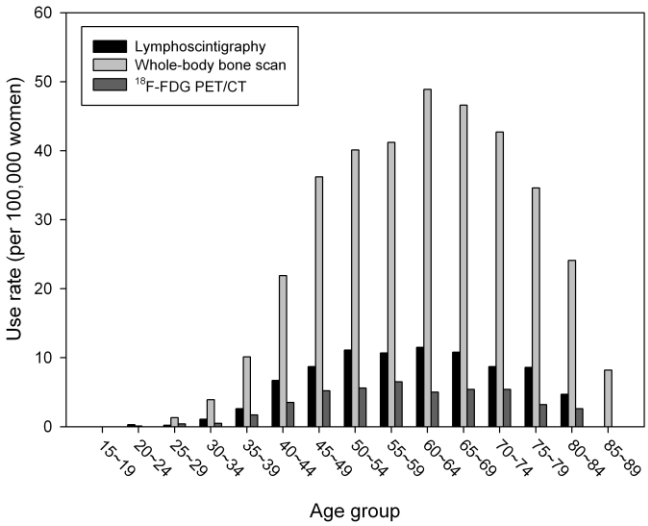

Figure 2. The age distribution of each of the three nuclear medicine procedures in patients with late-stage breast cancer in Taiwan, 2012 according to NHIRD.

Based on multiple linear regression analysis, where the mortality of breast cancer was variably dependent, the prevalence of early-stage or late-stage breast cancer and the rate of nuclear medicine procedures used were independent variables. In patients with late-stage breast cancer, the mortality of breast cancer significantly increased with the pre-

Table 3. *Multivariate regression model for the mortality of breast cancer according to NHIRD.*

Variables	b	SE	95% CI		P value
Intercept	4.02	3.84	-4.43	12.48	0.318
Prevalence of late-stage breast cancer	2.87	0.62	1.51	4.24	0.001
Use rate of whole-body bone scan in patients with late-stage breast cancer	-4.28	1.14	-6.79	-1.77	0.003

valence of the disease (b=2.87, P=0.001) and significantly decreased when using whole-body bone scan (b=-4.28, P=0.003), as shown in Table 3. However, no significant correlation existed in patients with late-stage breast cancer between the mortality of breast cancer and the use of the other two nuclear medicine procedures. In early-stage breast cancer patients, no significant correlation was found between breast cancer mortality and the use of all three nuclear medicine procedures.

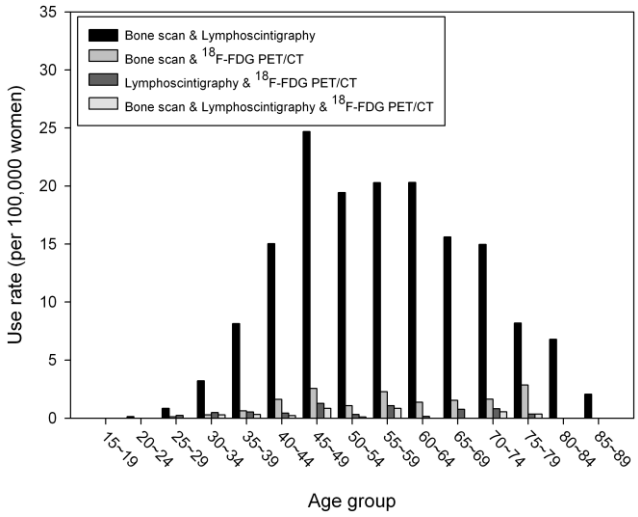

Figure 3. The age distribution of two joint nuclear medicine procedures in patients with early-stage breast cancer in Taiwan, 2012 according to NHIRD.

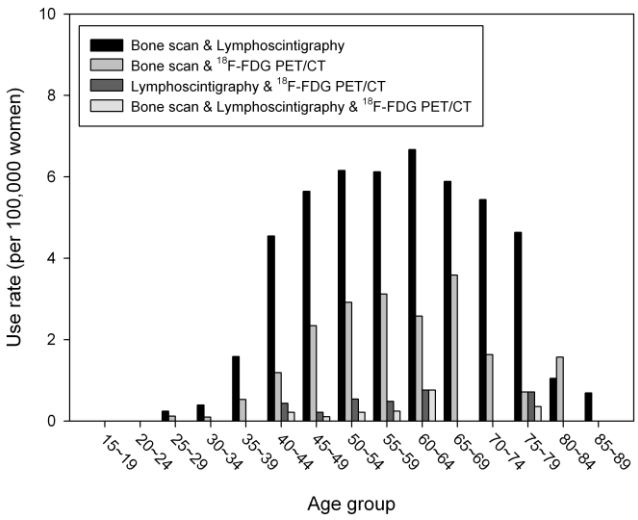

Figure 4. The age distribution of two together multiple nuclear medicine procedures in patients with late-stage breast cancer in Taiwan, 2012 according to NHIRD.

Discussion

Because the 5 years survival rate of breast cancer is approximately 70% in East Asia as reported for 2014 [9], we analyzed the effect of the utilization of nuclear medicine procedures and the mortality of breast cancer after 5 years, in 2017.

Additionally, because cancer stages are not recorded in the NHIRD, we separated early- and late-stage breast cancer by selecting patients who were undergoing partial mastectomy and mastectomy, respectively as being at an early or late state of the disease.

The mortality of breast cancer has been related to cancer staging [10], i.e., higher mortality was correlated with advanced breast cancer; thus, in this study, the prevalence of mastectomy was positively associated with mortality of breast cancer and was regarded as a confounder to be controlled. Therefore, in patients with late-stage breast cancer the significantly negative correlation between the use of whole-body bone scan and breast cancer mortality was shown after adjusting the confounding factor in the multivariate model.

Axillary lymph node dissection (ALND) can be avoided in patients with early breast cancer and limited sentinel-node involvement, thereby eliminating complications, particularly lymph edema, sensory loss, and shoulder abduction deficits [11]. Lymphoscintigraphy, which is used to map the distribution of sentinel lymph nodes (SLN) for biopsy and identify the regional nodal status, can assist to avoid total lymph modes dissection when a negative sentinel node is found in the axilla [12]. Recent studies avoid total lymph modes dissection mainly when sentinel node in axilla is negative. In this study, ALND was performed in 1,861 cases of early-stage breast cancer without lymphoscintigraphy, accounting for 53.7% of this population. However, another 1,183 early-stage breast cancer patients underwent ALND after receiving lymphoscintigraphy, accounting for only 43.3% of this population, which is significantly less than the group which did not have lymphoscintigraphy. Thus, lymphoscintigraphy did help surgeons to accurately identify regional lymph nodal status of breast cancer and avoid unnecessary ALND if no metastasis was found in the sentinel node.

The most common distant metastases of breast cancer are the bones, liver, and lungs [13]. Whole-body bone scan is the most commonly used modality to detect bone metastases in breast cancer. It is effective, noninvasive, low-cost, and provides valuable diagnostic and prognostic information of breast cancer [14]. According to a meta-analysis, the pooled sensitivity and specificity of whole-body bone scan for detecting

bony metastases of breast canceris approximately 81% (33%-100%) and 96% (55%-100%), respectively [15]. In the late-stage breast cancer population of this study, 1,711 of 2,221 patients with whole-body bone scan underwent chemotherapy (77.0%) and 707 patients underwent radiotherapy (31.8%). However, only 1,109 of 1,844 patients without whole-body bone scan underwent chemotherapy (60.1%) and 289 patients underwent radiotherapy (15.7%). This could be due to the gravity of the disease but also relates to the fact that whole-body bone scan can accurately detect bone metastases of breast cancer, thus suggesting the necessary chemotherapy or radiotherapy treatment and reducing overall mortality. Whole-body bone scan seems to play an important role in the management of advanced breast cancer.

The prevalence of hepatic and pulmonary metastases is reported to beless than 1% in early breast cancer. Thus, ^{18}F-FDG PET/CT is not indicated in subjects with apparently early stage I or II of breast cancer [16]. However, it is a reasonable alternative for following-up cases with suspicious or equivocal computed tomography or magnetic resonance imaging findings. In this study, the utilization of single or combined ^{18}F-FDG PET/CT accounted for only 3.5% of patients with early-stage breast cancer and 7.4% of patients with late-stage breast cancer. The use of ^{18}F-FDG PET/CT was not associated with the mortality of breast cancer, probably due to the low frequency of using this modality.

In conclusion, as from the data derived from NIHIRD in Taiwan, the mortality of women with late-stage breast cancer was negatively related to the utilization of whole-body bone scan but not to the utilization of lymphoscintigraphy or the ^{18}F-FDG PET/CT scan. In women with early-stage breast cancer, no significant correlation existed between breast cancer mortality and the utilization of the above three nuclear medicine procedures.

The authors declare that they have no conflicts of interest.

Bibliography

1. Cancer today, World Health Organization. http://gco.iarc.fr/today/home. Accessed 10 Oct 2018.
2. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer* 2013; 49: 1374-403.
3. Dupont EL, Kamath VJ, Ramnath EM et al. The role of lymphoscintigraphy in the management of the patient with breast cancer. *Ann Surg Oncol* 2001; 8: 354-60.
4. Alex JC, Krag DN. Gamma-probe guided localization of lymph nodes. *Surg Oncol* 1993; 2: 137-43.
5. Mavriopoulou E, Zampakis P, Smpiliri E et al. Whole body bone SPET/CT can successfully replace the conventional bone scan in breast cancer patients. A prospective study of 257 patients. *Hell J Nucl Med* 2018; 21(2): 125-33.
6. Cook GJ, Houston S, Rubens R et al. Detection of bone metastases in breast cancer by ^{18}F-FDG PET/CT: differing metabolic activity in osteoblastic and osteolytic lesions. *J Clin Oncol* 1998; 16: 3375-9.
7. Mittal BR, Manohar K, Kashyap R et al. The role of ^{18}F-FDG PET/CT in initial staging of patients with locally advanced breast carcinoma with an emphasis on M staging. *Hell J Nucl Med* 2011; 14(2):135-9.
8. Derks MGM, Bastiaannet E, van de Water W et al. Impact of age on breast cancer mortality and competing causes of death at 10 years follow-up in the adjuvant TEAM trial. *Eur J Cancer* 2018; 99: 1-8.
9. Che Y, You J, Zhou S et al. Comparison of survival rates between Chinese and Thai patients with breast cancer. *Asian Pac J Cancer Prev* 2014; 15: 6029-33.
10. Breast Cancer: Statistics. Cancer.Net. https://www.cancer.net/cancer-types/breast-cancer/statistics/2015. Accessed 10 Oct 2018.
11. Giuliano AE, Hunt KK, Ballman KV et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA* 2011; 305: 569-75.
12. Iakovou IP, Giannoula E.Nuclear medicine in diagnosis of breast cancer. *Hell J Nucl Med* 2014; 17(3): 221-7.
13. Myers RE, Johnston M, Pritchard K et al. Baseline staging tests in primary breast cancer: a practice guideline. *CMAJ* 2001; 164: 1439.
14. Puglisi F, Follador A, Minisini AM et al. Baseline staging tests after a new diagnosis of breast cancer: further evidence of their limited indications. *Ann Oncol* 2005; 16: 263-6.
15. Rong J, Wang S, Ding Q et al. Comparison of ^{18}FDG PET/CT-CT and bone scintigraphy for detection of bone metastases in breast cancer patients. A meta-analysis. *Sur Oncol* 2013; 22: 86-91.
16. Ravaioli A, Pasini G, PolselliA et al. Staging of breast cancer: new recommended standard procedure. *Breast Cancer Res Treat* 2002; 72: 53-60.