

Relation between primary tumor FDG avidity and site of first distant metastasis in patients with breast cancer

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Abstract

Identification of tumor imaging features associated with metastatic pattern may allow better understanding of cancer dissemination. Here, we investigated how primary tumor ¹⁸F-fluorodeoxyglucose (FDG) avidity influences the first site of breast cancer metastasis.

Subjects were 264 patients with advanced breast cancer who underwent positron emission tomography/computed tomography at diagnosis and had metastasis at presentation (n=193) or metastatic relapse after surgery (n=71). Primary tumor FDG avidity (maximum SUV [SUV_{max}] ≥10.1) was compared with histology and first metastatic sites.

The most common site of first metastasis was the bone, occurring in 62.7% of patients with metastasis at presentation and 38.0% of those with metastatic relapse. First metastasis to lung occurred in 30.1% and 35.2%, and to liver in 25.4% and 15.2% of respective groups. In patients with metastasis at presentation, primary tumors were FDG avid in 98/193 cases, and this was associated with more frequent first metastasis to lung (37.8% vs 22.1%; *P*=0.018). In patients with metastasis relapse, primary tumors were FDG avid in 31/71 cases, and this was associated with more frequent first metastasis to lung (48.4% vs 25.0%; *P*=0.041) and liver (29.0% vs 5.0%; *P*=0.008). In patients with metastasis relapse, primary tumors that were FDG avid but hormone receptor negative had more first metastasis to lung (57.9% vs 26.9%; *P*=0.016).

FDG-avid primary breast tumors have favored first spread to the lung and liver, which suggests that tumor cells with heightened glycolytic activity better colonize these organs.

Abbreviations: FDG = ¹⁸F-fluorodeoxyglucose, HR = hormone receptor, LN = lymph node, PET/CT = positron emission tomography/computed tomography, SUV = standard uptake value, SUV_{max} = maximum SUV.

Keywords: breast cancer, FDG, hormone receptor, metastatic site, PET/CT

1. Introduction

Breast cancer is the most common cancer in women and the leading cause of cancer-related mortality.^[1] Dissemination of

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breast cancer to other organs may be detected at initial presentation or may occur as metastatic relapse years after patients receive curative surgery.^[1] Distant metastasis, rather than primary breast tumor, is the main cause of patient death. Accordingly, the presence and site of breast cancer metastasis is of crucial importance to the clinical course and outcome of patients.^[2–4] In breast cancer, loco-regional spread is associated with substantially more favorable outcome compared with distant metastasis. Furthermore, even with distant metastasis, prognosis is significantly influenced by the site of first spread. Among preferential sites for breast cancer dissemination, metastases to the liver or lung have been shown to lead to poorer patient outcome compared with the bone.^[5,6]

Metastasis occurs by cancer cell migration to target tissue and their subsequent survival and proliferation. The “seed” and “soil” hypothesis proposes that the distribution of metastatic spread is not a matter of chance but rather related to the biological compatibility between migrating tumor cells and receiving organ.^[6] Site-specific metastasis is thus critically influenced by the molecular characteristics of cancer cells originating from primary tumor and their interaction with target tissue microenvironment. In breast cancer, tumor subtype has been implicated to influence sites of metastasis,^[7] and higher tumor grade has been shown to be associated with spread to sites of more adverse prognosis such as lung or liver.^[8] However, tumor histology offers only weak outlooks on the pattern of metastasis. More recent studies are focusing on gene-expression signatures that are linked with risk of dissemination or with site-specific metastasis.^[9,10] However, any requirement for tissue sampling suffers from significant intratumor heterogeneity of

malignant as well as nonmalignant cells that comprise the tumor.^[11] Routine gene expression analysis may also be restricted by its availability, cost, and limited reproducibility.^[12] In breast cancer, there is also controversy regarding subjectivity of subtype classification^[13] and optimal cutoffs for receptor expression.^[14]

Positron emission tomography/computed tomography (PET/CT) is widely used for evaluating malignant tumors,^[15] where ¹⁸F-fluorodeoxyglucose (FDG) uptake serves as a marker for heightened glycolytic metabolism. In breast cancer patients, tumor FDG uptake level has been shown to correlate with tumor subtype, treatment response, and patient outcome.^[16] Unlike histopathologic tests, PET/CT imaging provides quantitative measurement of FDG uptake over the entire tumor volume in a simple, noninvasive, and reproducible manner. Moreover, PET/CT is often performed in cancer patients at initial presentation for tumor staging or evaluating treatment response. A previous study observed higher FDG uptake in breast cancers that developed distant metastasis compared with those that did not metastasize,^[17] suggesting a link between primary tumor glycolytic activity and risk of metastasis. Given that target tissue microenvironment is likely to place specific metabolic demands to invading cells, the glycolytic phenotype of primary breast tumors may also influence its preferred site of metastasis. Uncovering such relations could improve our understanding of the mechanisms of sites-specific tumor spread and help identify new therapeutic targets.

In this study, we thus investigated whether primary tumor FDG avidity is associated with the first site of distant spread in advanced breast cancer. This was tested in patients who already had metastasis at the time of initial diagnosis as well as those who developed metastatic relapse following curative resection.

2. Materials and methods

2.1. Study population

Study subjects were selected from 1415 patients who underwent palliative chemotherapy for advanced breast cancer at our institute. Among these, 299 patients who underwent FDG PET/CT at the time of initial diagnosis were included as study candidates. As this study was focused on distant metastasis, we excluded 17 cases with only regional chest wall or lymph node (LN) involvement. We also excluded 8 patients who had concurrent ($n=3$) or previous malignancies ($n=5$). Thus, a total of 274 subjects were finally included for analysis. This retrospective study was approved by Samsung Medical Center Institutional Review Board and the requirement for written consents was waived.

The study subjects were categorized either as patients who had metastatic disease at the time of initial presentation ($n=193$), or those who developed metastatic relapse during follow-up after curative resection ($n=71$). There were an additional 10 cases that did not show metastasis at initial diagnosis, but displayed metastatic disease after neoadjuvant chemotherapy. These cases were not included in the analysis but were assessed separately.

2.2. FDG PET/CT imaging

All patients fasted for at least 6 hours and had blood glucose levels of <200 mg at the time of PET/CT. Imaging was performed 60 minutes after injection of 5 MBq/kg FDG without intravenous or oral contrast on a Discovery LS or a Discovery STe PET/CT

scanner. Whole-body CT was performed with a continuous spiral technique with an 8-slice helical CT (140 keV; 40–120 mA; Discovery LS) or a continuous spiral technique with 16-slice helical CT (140 keV; 30–170 mA; Discovery STe). After the CT scan, an emission scan was obtained from head to thigh for 4 minutes per frame in 2D mode with reconstruction of attenuation-corrected PET images ($4.3 \times 4.3 \times 3.9$ mm) using an ordered-subset expectation maximization algorithm (28 subsets, 2 iterations; Discovery LS), or for 2.5 minutes per frame in 3D mode with reconstruction of attenuation-corrected PET images ($3.9 \times 3.9 \times 3.3$ mm) using a 3D ordered-subset expectation maximization algorithm (20 subsets, 2 iterations; Discovery STe).

2.3. PET image analysis

On transaxial PET images, a circular region of interest was placed on breast tumors, and maximum standardized uptake values (SUVmax) of FDG uptake were measured. The threshold for FDG avidity was based on the mean SUVmax among subjects with metastatic relapse (SUVmax=10.1). This was because any influence of metastatic tumor on primary tumor FDG uptake could be excluded in this group. This threshold for FDG avidity was also applied to patients with metastasis at presentation.

2.4. Characterization of primary tumors and metastatic lesions

Clinical information including tumor histology and metastatic sites was obtained from medical records. Tumor subtype was histologically determined. Tumors expressing both estrogen and progesterone receptors were considered hormone receptor (HR) positive. Tumor size was based on MRI, but CT, ultrasound or mammographic measurements were used if MRI was not available. Whole breast involvement was treated as a 10 cm-sized tumor.

Metastatic sites were determined by pathology or conclusive imaging findings. In 1 patient, liver metastasis was based on strong clinical evidence that led to additional treatment. Involvement of LNs other than axillary, internal mammary, or supraclavicular were considered distant metastasis. When more than 1 metastatic lesion was detected at the same time, it was not possible to determine which lesion occurred first, and all of the lesions were treated as the first metastatic site.

2.5. Statistical analysis

Significance of difference in characteristics according to tumor FDG avidity was assessed by Student's t tests, Pearson χ^2 tests, or Fisher's exact tests. Difference in frequency of metastasis to the specific sites was analyzed by χ^2 or Fisher's exact tests. SPSS software for Windows was used for statistical analysis. P values < 0.05 were considered statistically significant.

3. Results

3.1. Characteristics of study subjects

The clinical characteristics of the "metastasis at presentation" group ($n=193$) are summarized in Table 1. These patients had a mean age of 52.7 ± 11.0 years, primary tumor size of 6.3 ± 3.4 cm, and HR-positive rate of 59.6%. The primary tumor had an average SUVmax of 10.6 ± 5.4 , and 98/193 tumors (50.8%) were FDG avid (SUVmax ≥ 10.1). Patients with FDG-avid primary

Table 1
Characteristics of breast cancer patients with “metastasis at presentation” categorized according to primary tumor FDG avidity.

	Total (n=193)	FDG nonavid primary tumor (n=95)	FDG-avid primary tumor (n=98)	P value
Age, y (mean ±SD)	52.7 ± 11.0	54.5 ± 11.0	50.9 ± 10.8	0.022*
SUVmax (mean ±SD)	10.6 ± 5.4	6.4 ± 2.9	14.6 ± 4.1	0.000*
Tumor size, cm (mean ±SD)	6.3 ± 3.4	5.6 ± 3.3	7.0 ± 3.2	0.003*
Hormone receptor status				0.114 [†]
Receptor positive	115 (59.6%)	62 (65.3%)	53 (54.1%)	
Receptor negative	78 (40.4%)	33 (34.7%)	45 (45.9%)	
Histology				1.000 [‡]
Invasive ductal cancer	192 (99.5%)	94 (99.0%)	98 (100%)	
Invasive lobular cancer	1 (0.05%)	1 (1.0%)	0 (0%)	

FDG = ¹⁸F-fluorodeoxyglucose, LN = lymph node, SD = standard deviation, SUVmax = maximum standard uptake value.

* t test.

[†] Pearson χ^2 test.

[‡] Fisher's exact test.

The significance of Bold values $P < 0.05$.

tumors were slightly younger than those with nonavid tumors. FDG-avid primary tumors were slightly larger than nonavid tumors, but there was no significant difference in tumor subtype or histology according to FDG avidity.

The clinical characteristics of the “metastatic relapse” group (n = 71) are summarized in Table 2. These patients had a mean age of 48.9 ± 9.7 years; primary tumor size of 5.9 ± 2.9 cm; and HR positive rate of 38.0%. The primary tumor had an average SUVmax of 10.1 ± 4.7, and 31/71 tumors (43.7%) were FDG avid (SUVmax ≥ 10.1). Patients with FDG-avid and nonavid primary tumors showed no significant difference in age, tumor size, histology, stage, or premetastasis treatment.

In addition to the 2 groups described above, there were 10 cases that showed no evidence of metastasis at presentation but revealed metastatic disease after neoadjuvant chemotherapy. The primary tumor was FDG-avid in 8 cases and nonavid in 2 cases. Only 1 tumor was HR positive. The metastatic site was visceral organ in 7 cases, distant LNs in 2 cases, and bone in 1 case.

3.2. The “metastasis at presentation” group

In this group of 193 patients, 114 had a single site of metastasis at presentation (59.1%), 68 had 2 sites (35.2%), and 11 had ≥ 3 sites (5.7%). In subjects with ≥ 2 metastatic lesions at presentation, it could not be determined which occurred first, and all were treated as first sites of metastasis. The most common first site of metastasis was the bone, which was present in 121 subjects (62.7%). This was followed in frequency by the lung (30.1%), liver (25.4%), and distant LNs (18.7%).

In this group, patients with FDG-avid primary tumors were significantly more likely to have first dissemination to the lung compared with those with nonavid tumors (Table 3). There was no difference in frequency of first metastasis to the bone according to primary tumor FDG avidity (Table 3). FDG PET/CT findings of a representative case with FDG-avid primary breast cancer and lung metastasis at initial presentation are illustrated in Fig. 1.

Unlike FDG avidity, patients with primary tumors who were HR positive were significantly more likely to have first metastasis to the bone (68.7% vs 53.9%) and significantly less likely to have

Table 2
Characteristics of breast cancer patients with “metastatic relapse” categorized according to primary tumor FDG avidity.

	Total (n = 71)	FDG nonavid primary tumor (n = 40)	FDG-avid primary tumor (n = 31)	P value
Age, y (mean ±SD)	48.9 ± 9.7	49.7 ± 8.7	48.0 ± 11.1	0.475 [†]
SUVmax (mean ±SD)	10.1 ± 4.7	7.1 ± 2.4	13.9 ± 4.1	0.000[†]
Interval to metastasis, mo	21.2 ± 12.7	20.3 ± 12.1	22.4 ± 13.4	0.490 [†]
Tumor size, cm (mean ±SD)	5.9 ± 2.9	5.7 ± 2.9	6.1 ± 3.1	0.489 [†]
Hormone receptor status				0.917 [‡]
Receptor positive	27 (38.0%)	15 (37.5%)	12 (38.7%)	
Receptor negative	44 (62.0%)	25 (62.5%)	19 (61.3%)	
Histology and stage	71 (100%)	40 (100%)	31 (100%)	–
Invasive ductal cancer	71 (100%)	40 (100%)	31 (100%)	–
T stage, 0–1 vs 2–4 [*]	24 vs 48	16 vs 24	7 vs 24	0.120 [‡]
N stage, 0–1 vs 2–3 [*]	34 vs 37	14 vs 26	20 vs 11	0.014[‡]
Treatment before metastasis				0.920 [§]
Surgical resection	71 (100%)	40 (100%)	31 (100%)	
Neoadjuvant chemotherapy	67 (94.4%)	37 (92.5%)	30 (96.8%)	
Adjuvant chemotherapy	4 (5.6%)	3 (7.5%)	1 (3.2%)	
Radiotherapy	67 (94.4%)	36 (90.0%)	31 (100%)	

FDG = ¹⁸F-fluorodeoxyglucose, LN = lymph node, SD = standard deviation, SUVmax = maximum standard uptake value.

* p or yp.

[†] t test.

[‡] Pearson χ^2 test.

[§] Fisher's exact test.

The significance of Bold values $P < 0.05$.

Table 3
First organ of metastasis in the “metastasis at presentation” group according to primary tumor FDG avidity or hormone receptor status.

Metastatic site	Total (n=193)	FDG nonavid primary tumor (n=95)	FDG-avid primary tumor (n=98)	P value
Lung	58 (30.1%)	21 (22.1%)	37 (37.8%)	0.018*
Liver	49 (25.4%)	23 (24.2%)	26 (26.5%)	0.710*
Brain	4 (2.1%)	1 (1.1%)	3 (3.1%)	0.621*
Bone	121 (62.7%)	60 (63.2%)	61 (62.3%)	0.896*
Lymph node	36 (18.7%)	20 (21.1%)	16 (16.3%)	0.399*
Pleural/peritoneal	7 (3.6%)	5 (5.3%)	2 (2.0%)	0.274†
Metastatic site	Total (n=193)	Hormone (+) primary tumor (n=115)	Hormone (-) primary tumor (n=78)	P value
Lung	58 (30.1%)	35 (30.4%)	23 (29.5%)	0.888*
Liver	49 (25.4%)	26 (22.6%)	23 (29.5%)	0.281*
Brain	4 (2.1%)	3 (2.6%)	1 (1.3%)	0.649†
Bone	121 (62.7%)	79 (68.7%)	42 (53.9%)	0.036*
Lymph node	36 (18.7%)	15 (13.0%)	21 (26.9%)	0.015*
Pleural/peritoneal	7 (3.6%)	4 (3.5%)	3 (3.9%)	1.000†

FDG = ¹⁸F-fluorodeoxyglucose.

* Pearson χ^2 test.

† Fisher's exact test.

The significance of Bold values $P < 0.05$.

first metastasis to distant LNs (13.0% vs 26.9%; Table 3). When we evaluated the risk of metastasis to specific organs according to a combination of FDG avidity and HR status, no significant difference in pattern of site-specific metastasis was observed in this group.

3.3. The “metastatic relapse” group

In this group of 71 patients, 49 subjects (69.0%) had a single site of distant metastasis when recurrence was detected. Of the remaining, 14 had 2 sites (19.7%), and 8 had ≥ 3 sites of distant metastasis (11.3%). Again, all of these lesions were treated as

sites of first metastasis. The most common site of first metastatic recurrence was the bone that occurred in 27 cases (38.0%).

Patients among this group with FDG-avid primary tumors were significantly more likely to have first metastasis to the lung or liver compared with those with nonavid tumors (Table 4). There was no difference in frequency of first metastasis to the bone according to primary tumor FDG avidity (Table 4). FDG PET/CT findings of a representative case with FDG nonavid primary breast cancer that later recurred as bone metastasis, and a case with FDG-avid primary breast cancer that later recurred as liver metastasis are illustrated in Figs. 2 and 3, respectively.

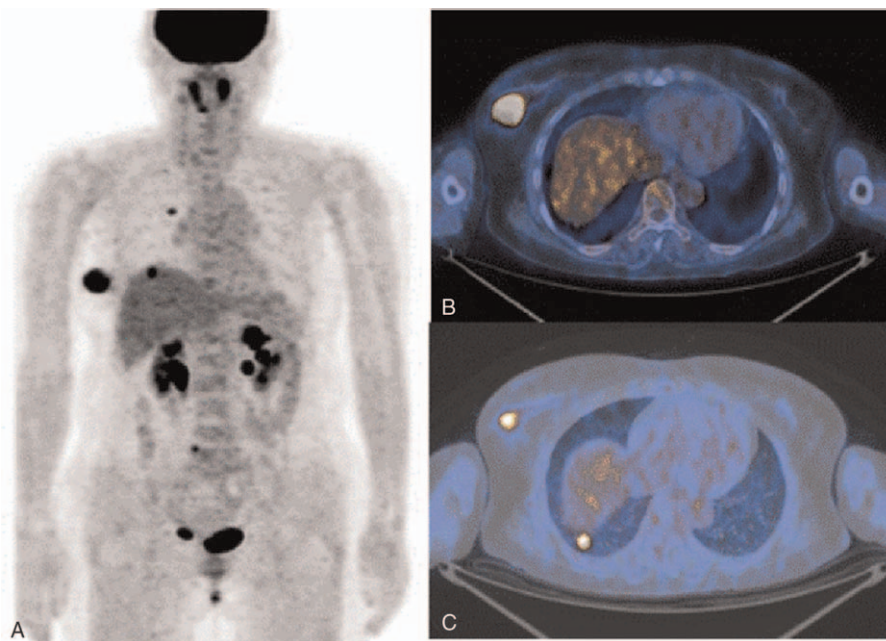


Figure 1. Representative PET/CT images of a 64-year-old female with an FDG-avid breast cancer and metastasis at initial presentation. (A) Projection and (B, C) transaxial images show right breast cancer with lung metastasis. The primary tumor had a SUVmax of 11.4 and was categorized as FDG avid (SUVmax ≥ 10.1). Metastatic pulmonary nodules were detected in the right lung (A, C), and the patient underwent palliative chemotherapy. FDG = ¹⁸F-fluorodeoxyglucose, PET/CT = positron emission tomography/computed tomography, SUVmax = maximum SUV standard uptake value.

Table 4

First organ of metastasis in the “metastatic relapse” group according to primary tumor FDG avidity or hormone receptor status.

Metastatic site	Total (n=71)	FDG nonavid primary tumor (n=40)	FDG-avid primary tumor (n=31)	P value
Lung	25 (35.2%)	10 (25.0%)	15 (48.4%)	0.041*
Liver	11 (15.5%)	2 (5.0%)	9 (29.0%)	0.008†
Brain	13 (18.3%)	10 (25.0%)	3 (9.7%)	0.128†
Bone	27 (38.0%)	15 (37.5%)	12 (38.7%)	0.917*
Lymph node	25 (35.2%)	14 (35.0%)	11 (35.5%)	0.966*
Pleural/peritoneal	2 (2.8%)	1 (2.5%)	1 (3.2%)	1.000†

Metastatic site	Total (n=71)	Hormone (+) primary tumor (n=27)	Hormone (-) primary tumor (n=44)	P value
Lung	25 (35.2%)	10 (37.0%)	15 (34.1%)	0.801*
Liver	11 (15.5%)	4 (14.8%)	7 (15.9%)	1.000†
Brain	13 (18.3%)	3 (11.1%)	10 (22.7%)	0.344†
Bone	27 (38.0%)	15 (55.6%)	12 (27.3%)	0.017*
Lymph node	25 (35.2%)	6 (22.2%)	19 (43.2%)	0.073*
Pleural/peritoneal	2 (2.8%)	0 (0.0%)	2 (4.6%)	0.522†

FDG = ¹⁸F-fluorodeoxyglucose.

* Pearson χ^2 test.

† Fisher's exact test.

The significance of Bold values $P < 0.05$.

Patients among this group with HR-positive primary tumors were significantly more likely to have first metastasis to the bone (55.6% vs 27.3%), compared with those with HR-negative tumors (Table 4). First metastasis to distant LNs had a trend for higher frequency in patients with HR-negative tumors (43.2% vs 22.2%, $P = 0.07$; Table 4). When we evaluated the risk of metastasis to specific organs according to a combination of FDG avidity and HR status, those with FDG-avid but HR-negative primary tumors were significantly more likely to have lung

metastasis (11/19; 57.9%) compared with the remaining patients (14/52; 26.9%; $P = 0.016$).

4. Discussion

In this study, we tested the hypothesis that primary tumor FDG avidity is associated with the preferred site of first distant spread in advanced breast cancer. Results in patients with metastatic disease at presentation revealed that first spread to the lung was

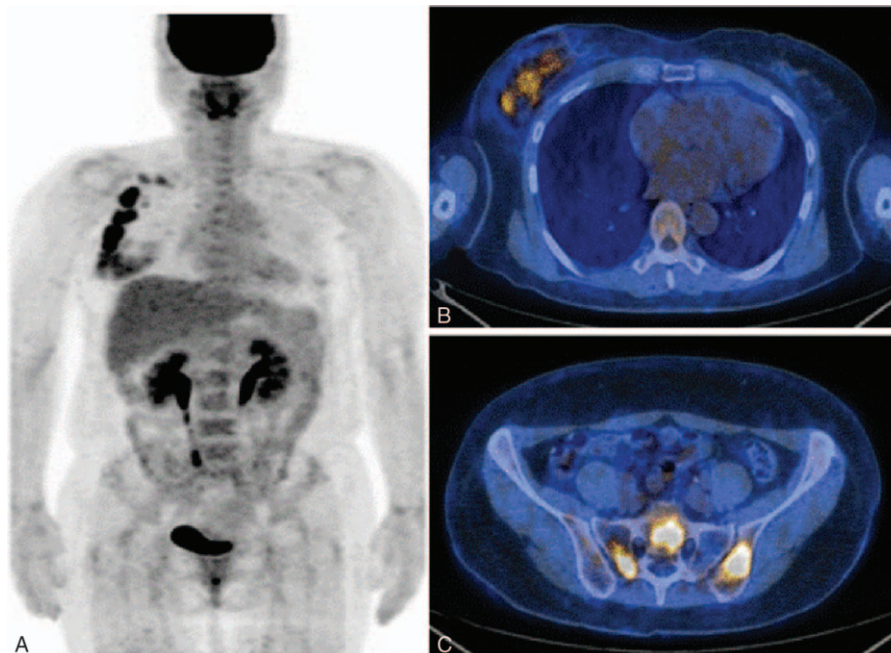


Figure 2. Representative PET/CT images of a 51-year-old female with a FDG nonavid breast cancer and metastatic recur to the bone. (A) Projection and (B) transaxial images show right breast cancer with ipsilateral axillary lymph node involvement. The primary tumor had a SUVmax of 4.5 and was categorized as FDG nonavid (SUVmax < 10.1). The patient received mastectomy with axillary lymph node dissection, chemotherapy and radiotherapy. (C) Follow-up FDG PET/CT 19 mo after the final treatment disclosed metastasis to iliac and sacral bones. FDG = ¹⁸F-fluorodeoxyglucose, PET/CT = positron emission tomography/computed tomography, SUVmax = maximum SUV standard uptake value.

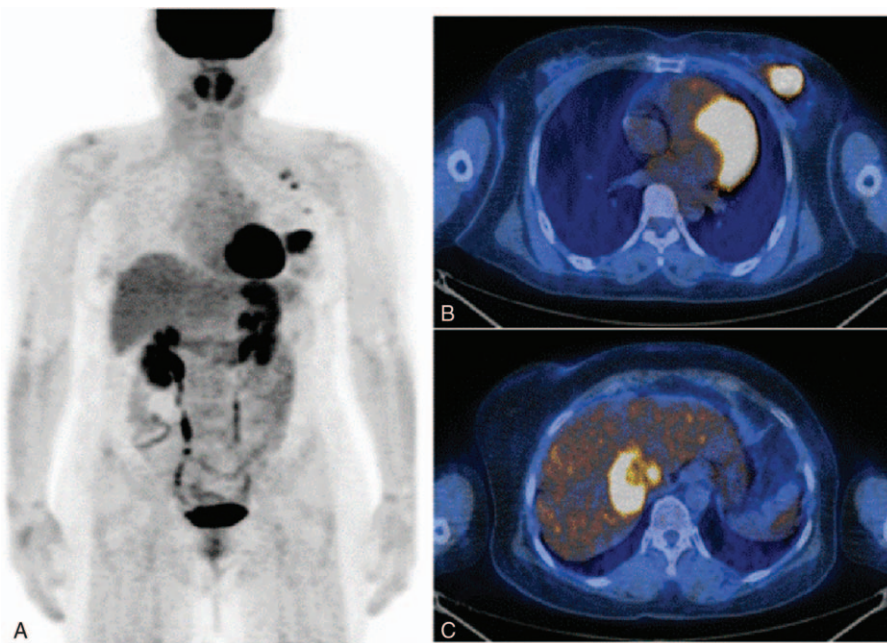


Figure 3. Representative PET/CT images of a 50-year-old female with a FDG-avid breast cancer and metastatic recur to the liver. (A) Projection and (B) transaxial images show left breast cancer with ipsilateral axillary lymph node involvement. The primary tumor had a SUVmax of 10.4 and was categorized as FDG avid (SUVmax ≥ 10.1). The patient underwent mastectomy with axillary lymph node dissection, chemotherapy and radiotherapy. (C) Follow-up PET/CT 1 year after the final treatment disclosed hepatic metastasis. FDG = ^{18}F -fluorodeoxyglucose, PET/CT = positron emission tomography/computed tomography, SUVmax = maximum SUV standard uptake value.

significantly more frequent in patients with FDG-avid compared with nonavid primary tumors. Furthermore, in subjects with metastatic relapse following curative surgery, first spread to the lung and liver was significantly more frequent in patients with FDG-avid primary tumors.

In both of our study populations, the most frequent distant site of first metastasis was the bone. When the 2 populations were compared, patients with metastatic disease at presentation had higher incidence of first metastasis to the bone, as well as the liver, compared with patients with metastatic relapse. This may be because there were more involved sites at the time of metastasis detection in the former group compared with the latter group. The strong preference of breast cancer to spread to the skeleton is well recognized.^[3–5] As site-specific metastasis occurs through interaction of tumor cells with tissue microenvironment, dominant dissemination to the bone indicates a favorable microenvironment for breast cancer cell colonization and growth. We found that the preference for bone metastasis was not influenced by primary tumor FDG avidity in either study groups. The bone marrow provides a rich micro-metastatic niche that is composed of myeloid-derived cells, adaptive immune cells, chemokines, and various stromal components.^[18] Our finding thus suggests that the favorable microenvironment of the bone allows both FDG-avid and nonavid breast cancer cells to spread and thrive equally well.

As with metastasis to the bone, risk of first metastasis to distant LNs and brain was also uninfluenced by primary tumor FDG avidity for both study groups. Distant LNs as the first site of metastasis were relatively common in our subjects, particularly considering their relatively small volume compared with major organs. Lymphatic spread is the most common route of metastasis for carcinomas, and subsequently, LNs are a frequent site for tumor cell transport and growth. Furthermore, lymphatic drainage into LNs of tumor-derived factors such as growth

factors and cytokines may help make this niche receptive of migrating tumor cells.^[19] The brain may also provide an environment rich in cytokines and growth factors derived by astrocytes, once tumor cells manage to pass the blood–brain barrier.^[20] Taken together, our findings suggest that favorable microenvironments of the bone, distant LNs, and brain may allow successful survival and proliferation of breast cancer cells with low as well as high glycolytic activity.

In contrast to organs with favorable local milieu, lung and liver tissues may be considered less favorable for tumor cells to evolve into metastatic colonies. Indeed, we found that first metastasis to the lung occurred significantly less often in both groups of patients when primary tumors were FDG nonavid compared with when they were FDG avid. This suggests the possibility that the inherent metabolic property of breast cancer cells may be a significant factor in determining the likelihood for metastasis to the lung. One possible link between glucose metabolism and metastatic characteristics of tumor cells is hypoxia-inducible factor 1 (HIF-1).^[21,22] High expression of HIF-1 in breast cancers has previously been shown to promote malignant progression and pulmonary metastasis.^[23,24] Cancer cells that migrate to the lung, where oxygen is relatively plentiful, are not likely to activate HIF-1 expression unless it is already driven by tumor phenotype. Given the strong association between HIF-1 and heightened glycolytic flux, the greater incidence of lung metastasis in patients with FDG-avid primary tumors in our study could reflect higher HIF-1 expression. A previous clinical study demonstrating higher FDG uptake in metastatic pulmonary cancers with high HIF-1 expression supports this possibility.^[25] However, such an association is only speculative, and further investigations will be required to clarify this issue.

In our study, first metastasis to the liver in patients with metastatic relapse was also significantly less frequent when primary tumor was FDG nonavid. The liver is the third most

common site for metastasis of breast cancer, and major breakthroughs have recently been achieved in understanding this process.^[26] As with pulmonary metastasis, HIF-1-regulated genes have been implicated in hepatic metastasis of breast cancers, supporting the possibility that the liver milieu may also favor growth of breast cancer cells with HIF-1 activation. Increased tumor FDG avidity may thus reflect cancer cell phenotypes that are better fit to thrive and proliferate in less favorable microenvironments. Although the reason why the association was weaker in patients with metastasis at presentation is not clear, it may be partly attributed to influence of metastatic tumor masses on primary tumor FDG uptake for this group. In addition, because 33 of the 49 liver metastases detected at diagnosis were accompanied by other metastatic sites, it is possible that at least in some of these cases, spread to the liver actually followed that of a different first metastatic site in this group.

We further compared the influence of primary tumor HR status on first metastatic sites. As a result, patients with HR-positive primary tumors had significantly greater frequency of first metastasis to the bone in both study groups. These results are consistent with previous reports that HR status can affect pattern of spread of breast cancer.^[27,28] For instance, patients with HR-positive breast cancer are known to be more likely to have bone metastasis.^[7,29–32] In our results, patients with HR-positive primary tumors had lower frequency of metastasis to distant LNs. Although previous studies have indicated a significant correlation between HR-negative status and the presence of positive axillary LNs,^[33] the relation between HR status and metastasis to distant LNs remains unclear. Divergent from bone or LN metastasis, the frequency of metastasis to other visceral organs in our study was not significantly influenced by HR status. Hence, we next evaluated whether combining the information of FDG avidity and HR status may help further stratify risk for site-specific metastasis. The results in patients with metastasis at presentation showed greater risk of first metastasis to the lung in subjects with primary tumors that are FDG avid but HR negative. This suggests the possibility that combining primary tumor FDG avidity and HR status may provide additional useful information.

In our study, preoperative PET/CT in breast cancer patients undergoing curative surgery discriminated FDG-avid from nonavid primary tumors. Among patients who later developed metastatic recurrence, those who had FDG-avid primary tumors turned out to have significantly greater likelihood of first relapse to the lung and liver compared to their counterparts. Therefore, although the level of breast cancer FDG uptake is not likely to guide the best mode of treatment, the presence of high uptake could guide clinicians to be more guarded against possible recurrence to the lung or liver following surgery. Furthermore, in patients with metastatic disease at presentation, recognition of the preferred sites for first metastasis according to primary tumor FDG avidity may help detect distant metastasis that might otherwise be missed. Hence, our findings suggest that assessment of primary breast cancer FDG avidity with pretreatment PET/CT offers information that may be helpful for patient management.

Limitations of our study include its retrospective design, which could have caused bias during selection and exclusion of study subjects. Also, a larger number of study subjects might have increased the statistic power to identify additional sites with significant difference between groups. Furthermore, all metastatic lesions present at the time of diagnosis were treated as “first

metastatic sites” even though some may have occurred later. However, this problem appears unavoidable in retrospective studies as our own. Finally, the optimum SUVmax threshold for primary tumor FDG avidity may require further confirmation in larger study populations.

5. Conclusions

In patients with breast cancer, the level of primary tumor FDG uptake is associated with different preferences for site of first dissemination either at initial presentation or during post-surgery follow-up. The favorable milieu of the bone appears to allow seeding of tumor cells regardless of their FDG avidity. In contrast, the favored spread of FDG-avid tumors to the lung and liver indicate that breast tumor cells with heightened glycolytic activity may be better fit to survive and grow in these microenvironments. Further investigations will be required to assess the precise role of tumor FDG avidity as a surrogate marker of breast cancer cell biology that is relevant to the site of first metastasis.

References

- [1] Chang J, Clark GM, Allred DC, et al. Survival of patients with metastatic breast carcinoma: importance of prognostic markers of the primary tumor. *Cancer* 2003;97:545–53.
- [2] Weigelt B, Peterse JL, van't Veer LJ. Breast cancer metastasis: markers and models. *Nat Rev Cancer* 2005;5:591–602.
- [3] Solomayer EF, Diel IJ, Meyberg GC, et al. Metastatic breast cancer: clinical course, prognosis and therapy related to the first site of metastasis. *Breast Cancer Res Treat* 2000;59:271–8.
- [4] Leone BA, Romero A, Rabinovich MG, et al. Stage IV breast cancer: clinical course and survival of patients with osseous versus extraosseous metastases at initial diagnosis. The GOCS experience. *Am J Clin Oncol* 1988;11:618–22.
- [5] Lee YT. Breast carcinoma: pattern of metastasis at autopsy. *J Surg Oncol* 1983;23:175–80.
- [6] Isaiah J. The pathogenesis of cancer metastasis: the ‘seed and soil’ hypothesis revisited. *Nat Rev Cancer* 2003;3:453–8.
- [7] Sihto H, Lundin J, Lundin M, et al. Breast cancer biological subtypes and protein expression predict for the preferential distant metastasis sites: a nationwide cohort study. *Breast Cancer Res* 2011;13:R87.
- [8] Porter GJ, Evans AJ, Pinder SE, et al. Patterns of metastatic breast carcinoma: influence of tumour histological grade. *Clin Radiol* 2004;59:1094–8.
- [9] van't Veer LJ, Dai H, van de Vijver MJ, et al. Gene expression profiling predicts clinical outcome of breast cancer. *Nature* 2002;415:530–6.
- [10] Minn AJ, Gupta GP, Siegel PM, et al. Genes that mediate breast cancer metastasis to lung. *Nature* 2005;436:518–24.
- [11] Martelotto LG, Ng CK, Piscuoglio S, et al. Breast cancer intra-tumor heterogeneity. *Breast Cancer Res* 2014;16:210.
- [12] Soni A, Ren Z, Hameed O, et al. Breast cancer subtypes predispose the site of distant metastases. *Am J Clin Pathol* 2015;143:471–8.
- [13] Schwartz GF, Bartelink H, Burstein HJ, et al. Adjuvant therapy in stage I carcinoma of the breast: the influence of multigene analyses and molecular phenotyping. *Breast J* 2012;18:303–11.
- [14] Reisenbichler ES, Lester SC, Richardson AL, et al. Interobserver concordance in implementing at 2010 ASCO/CAP recommendations for reporting ER in breast carcinomas: a demonstration of the difficulties of consistently reporting low levels of ER expression by manual quantification. *Am J Clin Pathol* 2013;140:487–94.
- [15] Farwell MD, Pryma DA, Mankoff DA. PET/CT imaging in cancer: current applications and future directions. *Cancer* 2014;120:3433–45.
- [16] Cintolo JA, Tchou J, Pryma DA. Diagnostic and prognostic application of positron emission tomography in breast imaging: emerging uses and the role of PET in monitoring treatment response. *Breast Cancer Res Treat* 2013;138:331–46.
- [17] Basu S, Mavi A, Cermik T, et al. Implications of standardized uptake value measurements of the primary lesions in proven cases of breast carcinoma with different degree of disease burden at diagnosis: does 2-deoxy-2-[F-18]fluoro-D-glucose-positron emission tomography predict tumor biology? *Mol Imaging Biol* 2008;10:62–6.

- [18] Kaplan RN, Rafii S, Lyden D. Preparing the “soil”: the premetastatic niche. *Cancer Res* 2006;66:11089–93.
- [19] Sleeman JP. The lymph node pre-metastatic niche. *J Mol Med* 2015;93:1173–84.
- [20] Sierra A, Price JE, García-Ramirez M, et al. Astrocyte-derived cytokines contribute to the metastatic brain specificity of breast cancer cells. *Lab Invest* 1997;77:357–68.
- [21] Dierckx RA, Van de Wuele C. FDG uptake, a surrogate of tumor hypoxia? *Eur J Nucl Med Mol Imaging* 2008;35:1544–9.
- [22] Semenza GL. Cancer-stromal cell interactions mediated by hypoxia-inducible factors promote angiogenesis, lymphangiogenesis, and metastasis. *Oncogene* 2013;32:4057–63.
- [23] Wong CC, Zhang H, Gilkes DM, et al. Inhibitors of hypoxia-inducible Factor 1 Block breast cancer metastatic niche formation and lung metastasis. *J Mol Med* 2012;90:803–15.
- [24] Zhang H, Wong CC, Wei H, et al. HIF-1-dependent expression of angiopoietin-like 4 and L1CAM mediates vascular metastasis of hypoxic breast cancer cells to the lungs. *Oncogene* 2012;31:1757–70.
- [25] Kaira K, Okumura T, Ohde Y, et al. Correlation between 18F-FDG uptake on PET and molecular biology in metastatic pulmonary tumors. *J Nucl Med* 2011;52:705–11.
- [26] Ma R, Feng Y, Lin S, et al. Mechanisms involved in breast cancer liver metastasis. *J Transl Med* 2015;13:64.
- [27] Maki DD, Grossman RI. Patterns of disease spread in metastatic breast carcinoma: influence of estrogen and progesterone receptor status. *Am J Neuroradiol* 2000;21:1064–6.
- [28] Kamby C, Rose C, Iversen H, et al. Patterns of metastases in human breast carcinoma in relation to estrogen receptor status. *Anticancer Res* 1986;6:107–12.
- [29] Koenders PG, Beex LV, Langens R, et al. Steroid hormone receptor activity of primary human breast cancer and pattern of first metastasis. The Breast Cancer Study Group. *Breast Cancer Res Treat* 1991;18:27–32.
- [30] Wei S, Li Y, Siegal GP, et al. Breast carcinomas with isolated bone metastases have different hormone receptor expression profiles than those with metastases to other sites or multiple organs. *Ann Diagn Pathol* 2011;15:79–83.
- [31] Kennecke H, Yerushalmi R, Woods R, et al. Metastatic behavior of breast cancer subtypes. *J Clin Oncol* 2010;28:3271–7; 94.
- [32] James JJ, Evans AJ, Pinder SE, et al. Bone metastases from breast carcinoma: histopathological–radiological correlations and prognostic features. *Br J Cancer* 2003;89:660–5.
- [33] Friedman NS, Freedman MD. Correlation of DNA flow cytometry and hormone receptors with axillary lymph node status in patients with carcinoma of the breast. *MD Med J* 1994;43:963–5.