Preoperative [18]fluorodeoxyglucose-positron emission tomography/computed tomography in early stage breast cancer: Rates of distant metastases

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Conflict-of-interest statement: The authors declare no conflicts of interests for this article.

Data sharing statement: No additional data are available.

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Manuscript source: Invited manuscript

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Received: March 28, 2017
Peer-review started: March 29, 2017
First decision: April 18, 2017
Revised: May 20, 2017
Accepted: June 19, 2017
Article in press: June 20, 2017
Published online: July 28, 2017

Abstract

AIM

To investigate rates of distant metastases (DM) detected with [18]fluorodeoxyglucose-positron emission
tomography/computed tomography (18FDG-PET/CT) in early stage invasive breast cancer.

METHODS
We searched the English language literature databases of PubMed, EMBASE, ISI Web of Knowledge, Web of Science and Google Scholar, for publications on DM detected in patients who had 18FDG-PET/CT scans as part of the staging for early stages of breast cancer (stage I and II), prior to or immediately following surgery. Reports published between 2011 and 2017 were considered. The systematic review was conducted according to the PRISMA guidelines.

RESULTS
Among the 18 total studies included in the analysis, the risk of DM ranged from 0% to 8.3% and 0% to 12.9% for stage I and II invasive breast cancer, respectively. Among the patients with clinical stage II, the rate of occult metastases diagnosed by 18FDG-PET/CT was 7.2% (range, 0%-19.6%) for stage IIA and 15.8% (range, 0%-40.8%) for stage IIB. In young patients (<40-year-old), 18FDG-PET/CT demonstrated a higher prevalence of DM at the time of diagnosis for those with aggressive histology (i.e., triple-negative receptors and poorly differentiated grade).

CONCLUSION
Young patients with poorly differentiated tumors and stage II B triple-negative breast cancer may benefit from 18FDG-PET/CT at initial staging to detect occult DM prior to surgery.

Key words: Breast cancer; Early stage; Staging workup; Distant metastases; [18]fluorodeoxyglucose-positron emission tomography/computed tomography scan

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Core tip: This systematic review identifies groups of patients with early stage breast cancer who might benefit most from [18]fluorodeoxyglucose-positron emission tomography/computed tomography (commonly known as 18FDG-PET/CT) scan at initial staging, prior to surgery.

Vinh-Hung V, Everaert H, Farid K, Djassemi N, Baudin-Veronique J, Bougas S, Michaïlovitch Y, Joachim-Contaret C, Cécilia-Joseph E, Verschraegen C, Nguyen NP. Preoperative [18]fluorodeoxyglucose-positron emission tomography/computed tomography in early stage breast cancer: Rates of distant metastases. World J Radiol 2017; 9(7): 312-320 Available from: URL: http://www.wjgnet.com/1949-8470/full/v9/i7/312.htm DOI: http://dx.doi.org/10.4329/wjr.v9i7.312

INTRODUCTION
Breast cancer is the most common cancer in women worldwide[1]. Mortality of breast cancer has declined notably in the United States, with death rates in 2012 decreasing 36% from peak rates as a result of improvements in early detection and treatment[2]. Yet, there remains considerable heterogeneity in the outcomes of early stage breast cancer[3-5]. The rate of death at 7 year due to stage I breast cancer was 2.1% in women aged 40 years or younger (as compared to 1.6% in women aged over 50) and was 3.8% in women with negative estrogen receptor status (as compared to 1.1% in those with positive estrogen receptor status)[3].

There is a large consensus that imaging should be limited to patients with apparent advanced disease or clinical suspicion of metastases[6-8]. Accordingly, staging scans are seldom performed[9,10]. The question arises, then, as to whether the excess mortality observed in “early stage” patients[11] is due to unfavorable biological factors or instead to the initial misclassification as “early stage”. We hypothesize that some clinically early stage breast cancer patients could benefit from a formal staging workup.

[18]fluorodeoxyglucose-positron emission tomography (18FDG-PET) scan is a valuable, well established tool for diagnostic staging in numerous cancer sites[9-12], as well as for locally advanced breast cancer to detect distant metastases (DM)[13-15]. Even though PET imaging is more sensitive for detection of loco-regional spread and metastatic disease in breast cancer compared to computed tomography (CT) scan alone, its high cost precludes the routine use of PET scan in clinical practice. Thus, a review of the literature is necessary for future guidelines about the benefit of PET scan in early stage breast cancer.

Standard-of-care for early stage breast cancer is surgery, either alone or followed by adjuvant radiotherapy and/or systemic therapy, depending on the pathologic stage and the type of surgery to be performed. The presence or absence of axillary lymph node metastases in patients with clinically non-palpable lymph nodes is routinely assessed through sentinel lymph node sampling or axillary lymph node dissection. Alternatively, PET scan could be most helpful in assessing the presence of DM in early stage breast cancer, which would preclude first-line surgery[16]. The prevalence of occult DM diagnosed by PET scan in patients with early stage breast cancer has not been analyzed and was the topic of this literature review. In particular, we sought to identify subsets of early stage breast cancer patients who might benefit most from PET scan, prior to surgery.

MATERIALS AND METHODS

Literature search strategy
Electronic searches were performed in the following databases: PubMed, EMBASE, ISI Web of Knowledge (Web of Science), and Google Scholar. The following terms were explored and used in each database search: “Breast cancer”, “surgery”, “PET scan”, “distant
metastases”, and “stage I (T1N0M0) and II (T0-2N1M0, T3N0M0)”. All relevant articles were accessed in full-text. The reference lists of relevant papers were then searched for additional publications.

Selection criteria
Eligible studies over the past 6 year (2011-2017) in the present review included those in which patients had 18FDG-PET/CT scan as part of their workup prior to or immediately after surgery for histologically-proven breast cancer, regardless of age or sex, and in which the rates of DM were reported by 18FDG-PET/CT scan. All patients had clinical stage I or stage II breast cancer. Only studies reported in English were considered. Duplicated studies were excluded.

Data extraction and critical appraisal
Prevalence of DM was extracted from each study and correlated to the disease stage. The influence of age, histology (e.g., lobular vs ductal), tumor grade (e.g., well differentiated vs poorly differentiated), and receptor status on the rate of DM (if reported) was also analyzed using descriptive summaries.

RESULTS
Number of reports analyzed
Figure 1 summarizes the search strategy. A total of 701 reports published between 2011 and 2017 were considered. Out of the 82 full papers that were assessed according to their potential for consisting of information relevant to the review, 18 were found to match the selection criteria and were selected for study inclusion. 18FDG-PET/CT scanning had been performed in addition to the clinical staging with or without conventional imaging in those 18 studies, either through a retrospective review or within a prospective protocol.

As none of the studies was randomized, bias could not be excluded. Publications reviewing patients with early stage invasive breast cancer were included.

Prevalence of DM diagnosed by 18FDG-PET/CT scan according to patient characteristics
Clinical stage: The rates of DM ranged from 0% to 30%[17-34] for the entire group of reported patients. However, only 9 of the studies correlated DM rates detected by 18FDG-PET/CT with the clinical stage[17,22,24,27,29,31,32,34]. The rate of DM was lowest among studies of patients with invasive lobular cancer compared to studies that had included a mixture of other histologies, such as invasive ductal carcinoma[18] (Tables 1 and 2).

Overall, the rate of DM for presumed stage I was low for all cancer types but non-negligible, ranging from 0% to 8.3%[22,27,29,31,32,34]. Among the 9 studies that reported the rate of DM in patients with stage II breast cancer separately, the prevalence ranged from 0% to 12.4%[17,22,24,27,29,31,32,34]. Patients with large tumors and/or axillary lymph node metastases appeared to be at increased risk of DM; specifically, the rate of DM was 7.2% (range, 0%-19.6%) and 15.8% (range, 0%-40.8%) for stage IIA and stage IIB, respectively[17,22,24,27,31,34].

Tumor size: Among studies that included a significant proportion of patients with large tumors (T2 and/or T3), the DM rate was higher and ranged from 8% to 8.4%[18,19], as compared to the range of 1.5% to 4.8% in studies including patients with smaller tumors[21,23,28]. However, since those latter studies also included a small proportion of patients with stage III disease and did not analyze the metastatic rate in relation to the clinical stage, the correlation between tumor size and DM rate remains unclear.

Nodal status: Patients who presented with N1 disease also presented with a higher risk of having DM. The rate of DM was 6% and 20% for N0 and N1 disease, respectively[21].

Receptor status: Among the 232 patients with triple-negative breast cancer, the DM rate was 0% and 10.9% for clinical stage I and stage II diseases, respectively[21]. However, there was no comparison performed with receptor-positive cases[22]. Other studies did not report the rates of DM according to receptor status.

Age: Two studies reported the influence of age on DM rate[27,28]. In the first study, among 134 young patients (< 40-year-old), the DM rate was 5% and 10.9% for clinical stage I and stage II, respectively[27]. In the second study, among 214 stage I-III patients, the DM rates did not differ significantly between the age groups of < 40-year-old and ≥ 40-year-old[28]. However, the DM rates in the younger age group were 8% in stage I, 9% in stage IIA and 17% in stage IIB, equating to 2x's
Table 1  Prevalence of distant metastases in patients with invasive breast cancer who had [18]fluorodeoxyglucose-positron emission tomography scan as part of the workup before or immediately after surgery

| Ref. | Subjects, n | Stage | Age, median | Histology | Tumor grade | Tumor receptors | Distant metastases | 2nd primaries |
|------|-------------|-------|-------------|-----------|-------------|----------------|-------------------|---------------|
| Groheux et al[15] | 131 | II: 84 III: 47 | NS | IDC: 114 ILC: 8 Other: 9 | 1: 9 2: 5 3: 53 NS: 4 | ER+: 82 HER2+: 30 | 5.90% (II) 1% (II) |
| Bernsdorf et al[16] | 103 | T2 or higher | 55 (24-81) | IDC: 83 ILC: 14 Other: 6 | 1: 11 2: 54 3: 37 NS: 1 | ER+: 74 HER+: 22 TN: 13 | 8% 1.90% |
| Choi et al[17] | 154 | 1: 69 II: 51 III: 21 IV: 13 T1: 89 T2: 51 T3: 14 | 52 (30-81) | IDC: 141 ILC: 4 Other: 9 | 1: 16 2: 50 3: 48 NS: 1 | ER+: 89 ER+: 26 | 6.90% 2.60% |
| Garami et al[18] | 115 | T1: 56 T2: 48 NS: 11 N0: 57 N+ 46 N+ 12 NS: 12 | 55.7 | IDC: 92 ILC: 11 Other: 12 | 1: 16 2: 50 3: 48 NS: 1 | ER+: 89 ER+: 26 | 6.90% 2.60% |
| Groves et al[19] | 70 | T1: 34 T2: 30 N1: 24 | 61 | IDC: 45 ILC: 10 Other: 5 | 1: 02 2: 33 3: 25 | ER+: 64 HER2+: 15 | 2.80% NS |
| Gunalp et al[20] | 141 | 1: 19 II: 100 III: 14 | 47 (28-78) | NS | 2 + 3: 141 | NS | 5% (II) 30% (II) NS |
| Pritchard et al[21] | 325 | T1: 207 T2: 110 T3: 8 N0: 325 | 56 (28-83) | IDC: 290 ILC: 35 | 1: 68 2: 158 3: 92 | NS | 1.50% NS |
| Cochet et al[22] | 142 | II: 79 III: 46 IV: 17 T2 or higher N0: 325 | 51 (25-85) | IDC: 128 ILC: 11 Other: 3 | 1+2: 81 3: 56 NS: 3 | ER+ / HER2+: 65 HER2+: 33 TN: 31 | 7.5% (II) NS |
| Jeong et al[23] | 178 | N0: 178 T1: 108 T2: 64 T3: 6 | 54.9 (33-82) | IDC: 145 ILC: 11 DCIS: 12 Other: 10 | 1: 21 2: 29 3: 09 NS: 3 | ER+/HER2+: 48 TN: 7 HER2+: 7 | 16% 3% |
| Koolen et al[24] | 62 | I: 35 II: 25 III: 2 T1: 62 | 59.8 (26-75) | IDC: 58 ILC: 1 Other: 3 | 1: 21 2: 29 3: 09 NS: 3 | ER+/HER2+: 48 TN: 7 HER2+: 7 | 16% 3% |
| Riedl et al[25] | 134 | I: 20 II: 91 III: 19 | 36.2 (22-39) | IDC: 124 ILC: 1 Other: 9 | 1: 01 2: 23 3: 110 | ER+ / HER2+: 75 HER2+: 26 | 5% (II) 10.9% (II) 4% |
| Zhang et al[26] | 164 | T1: 127 T2: 35 T3: 2 N0: 123 N1: 29 N2: 9 N3: 3 | 45 (21-70) | IDL: 150 ILC: 14 | 1: 23 2-3: 141 | ER+: 140 HER2+: 18 | 4.80% NS |
| Hogan et al[27] | 146 | I: 8 II: 50 III: 88 | 57 (34-92) | ILD: 146 | NS | ER+/HER2+: 132 HER2+: 8 TN: 5 | 0% (II) 4% (II) NS |
| Krammer et al[28] | 101 | II: 75 III: 15 IV: 11 T1: 7 | 54 | IDC: 80 ILC: 15 Other: 9 | 1: 05 2: 48 3: 45 NS: 6 | ER+: 67 HER2+: 56 | 15.80% NS |
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### Table 2  Prevalence of occult distant metastases in clinical stage II patients who had \(^{18}\text{FDG-PET/CT scan as part of a staging workup before or immediately after surgery}\)

| Ref. | Subjects, n | Age, median | II A | Distant metastases rate | All |
|------|-------------|-------------|------|-------------------------|-----|
| Groheux et al\(^{22}\) | 84 | NS | 2.80% (1/36) | 8.30% (4/48) | 5.95% |
| Guinalp et al\(^{34}\) | 100 | 51 | 19.60% (10/51) | 40.80% (20/49) | 30% |
| Cochet et al\(^{33}\) | 142 | 51 | 9.10% (2/22) | 7.00% (4/57) | 7.60% |
| Jeong et al\(^{31}\) | 70 | 54.9 | 0% (0/64) | 0% (0/6) | 0% |
| Riedl et al\(^{22}\) | 91 | 36.2 | 5% (2/44) | 17% (8/47) | 10.90% |
| Nursal et al\(^{31}\) | 315 | 51.5 | 9.50% (19/199) | 17.20% (20/116) | 12.40% |
| Ulaner et al\(^{32}\) | 169 | 51 | 5% (4/82) | 15% (13/87) | 9.50% |
| Lebon et al\(^{32}\) | 124 | 45.2 | 11% (7/64) | 15% (9/60) | 12.90% |
| Ulaner et al\(^{32}\) | 483 | 52.7 | 4.20% (6/143) | 13.80% (26/188) | 9.70% |
| All | 1578 | 47.8 | 7.20% (0%-19.6%) | 15.80% (0%-40.8%) | 11.40% (0%-12.9%) |

\(^{18}\text{FDG-PET: [18]fluorodeoxyglucose-positron emission tomography; NS: Not specified.}\)

Table 2 Prevalence of occult distant metastases in clinical stage II patients who had \(^{18}\text{FDG-PET/CT scan as part of a staging workup before or immediately after surgery}\)

DCIS: Ductal carcinoma in situ; ER: Estrogen receptor; \(^{18}\text{FDG-PET: [18]fluorodeoxyglucose-positron emission tomography; HER2: Human epidermal growth factor receptor 2; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; NS: Not specified; PR: Progesterone receptor; TN: Triple-negative.}\)

higher than those found in the first study.

**Histologic grade:** Histologic grade of the tumor may also be associated with increased risk of developing DM. Among 141 patients with moderate to poorly differentiated invasive breast cancers, the rate of DM was 30% for stage II patients\(^{22}\). However, correlation between tumor histologic grade and DM risk was not investigated in other studies\(^{[27-31,23,24,26-33]}\).

**DISCUSSION**

This article reviews the role of \(^{18}\text{FDG-PET/CT scan in the detection of DM in patients with early stages (i.e., I and II) of invasive breast cancer. The findings might represent important information applicable to discussions with patients about the utility of the scan. In contrast to stage III breast cancer, the role of \(^{18}\text{FDG-PET/CT scan in identifying patients with clinical stages I and II who are at high risk of DM is controversial. Even though \(^{18}\text{FDG-PET/CT scan may also be capable of identifying a second primary cancer, its main role in patients with breast cancer is the detection of DM, which could preclude upfront surgery\(^{[145]}\). Furthermore, the detection of DM could be of critical importance for the correct classification of patients and in the evaluation of treatment outcomes. As the risk of DM is low in "early stage" asymptomatic breast cancer patients, an expensive imaging study, such as with the \(^{18}\text{FDG-PET/CT scan, is not justified for the staging workup of all patients\[^{[6,35]}\]. However, breast cancer is a heterogeneous disease, with some subgroups of patients at risk of developing DM even at the early stage. Subgroups of breast cancer patients with worse outcome include younger patients\[^{[36]}\] and patients that have tumors with a more aggressive biological profile\[^{[37]}\]. Rare histologic subtypes, such as metaplastic carcinoma of breast and invasive micropapillary carcinoma, are also more frequently associated with poor prognosis because of the high**
rate of axillary lymph node involvement and DM\cite{38,39}. Genomic classification of risk, such as the oncotype DX and Perou’s studies, also identified the risk of distant recurrence\cite{40-42}. Thus, those patients at high risk of systemic spread may benefit from early diagnosis of DM, for which chemotherapy may be initiated in a timely manner and unnecessary surgery may be avoided. The benefit of $^{18}$FDG-PET scan may outweigh its cost in those circumstances.

In patients with clinical stage I breast cancer, regardless of age, tumor grade or aggressive histology, the risk of DM as diagnosed by $^{18}$FDG-PET scan ranged from 0% to 8.3%\cite{22,27,29,31,32,34}. This low, though not negligible, metastatic rate has been corroborated in studies with a high proportion of patients with T1 and N0 disease\cite{21,23}. Even though the number of patients with stage I disease in those studies was small, preliminary evidence suggested that $^{18}$FDG-PET scan may not be cost effective for clinical stage I patients.

In patients with clinical stage II breast cancer, the prevalence of occult DM detected through $^{18}$FDG-PET scan ranged from 0% to 12.4%\cite{17,22,24,27,29,31,32,34}. As stage II breast cancer patients also comprise a heterogeneous group, the risk of DM is higher for patients with stage II B disease (T3N0M0, T2N1M0) than for those with stage II A (T1N1M0, T2N0M0) disease. Discounting the one study that included only 6 patients with stage II B disease\cite{25}, the risk of unsuspected DM diagnosed by $^{18}$FDG-PET scan ranged from 2.8% to 19.6% for stage II A and 9.1% to 40% for stage II B, respectively\cite{17,22,27,31,32,34} (Table 2).

Patients with stage III B have larger tumors than those with stage II A. As tumor size has been reported to be correlated with an increased risk of DM, this may be one of the reasons underlying the higher rate of DM at diagnosis\cite{45}. Other studies have corroborated the increased prevalence of DM diagnosed with $^{18}$FDG-PET scan for patients with large tumors compared to those with smaller tumors\cite{18-21,23,28}. It is likely that other factors, like axillary lymph node metastases and tumor biology, may also lead to a high rate of DM at diagnosis\cite{22,24,27,29,31}.

Patients with triple-negative breast cancer frequently have a worse prognosis than their counterparts who harbor other subtypes because of the high rate of DM\cite{44}. A 10% rate of unsuspected DM was seen on $^{18}$FDG-PET scan compared to conventional imaging for patients with clinical stage II breast cancer\cite{32}. However, even among those triple-negative breast cancer patients, the risk of DM remained low for stage II A disease. Specifically, the DM rate was 5% and 15% for stage II A and II B triple-negative breast cancers, respectively.

Another prognostic factor that has been reported in the literature is the patient age at diagnosis. Young patients (< 40-year-old) may have a more aggressive tumor biology that translates to a lower survival rate compared to older patients\cite{36}. Among young patients with breast cancer, those with stage II B disease had a 17% rate of DM compared to 5% for stage II A. The incidence of DM in patients with clinical stage II A with moderate to poorly differentiated grade carcinoma climbs to 19.6% after $^{18}$FDG-PET scanning\cite{22}. Tumor biology needs to be taken into account beyond the conventional TNM staging. In patients with invasive micropapillary carcinoma, for example, a high rate of DM detected by $^{18}$FDG-PET scan before surgery has been reported. Among 16 patients with invasive micropapillary carcinoma who underwent $^{18}$FDG-PET scan when the tumor was diagnosed, axillary lymph node metastases and DM were observed in 12 (75% of cases)\cite{48}.

To date, this is the first study looking at the impact of $^{18}$FDG-PET on the management of invasive micropapillary carcinoma, a rare tumor with a high rate of axillary lymph node invasion and DM, even in the case of a relatively small tumor. Moreover, no study has been performed yet to investigate the role of $^{18}$FDG-PET scan for the diagnosis of occult DM in patients who had surgery for metastatic carcinoma of the breast, another rare tumor with a poor survival rate associated with a high propensity to metastasize to distant sites.

Our study was restricted by the limited availability of the data correlating clinical stages and biology with the risk of DM diagnosed with $^{18}$FDG-PET/CT scan in patients with early stage breast cancer. Ki-67 is a known prognostic marker\cite{46} but was not reported in any of the recent and largest studies\cite{31-34}. Most studies were retrospective. The classification of patients into stages was usually done after the $^{18}$FDG-PET/CT image acquisition, which might have affected the selection of patients. Some studies included the more advanced stages, stage III and IV, and a few studies included post-operative patients. Many issues of importance are relevant for breast cancer, notably the emerging role of PET/MRI and its comparison with PET/CT\cite{51,52}, the use of PET in the monitoring of neoadjuvant therapy\cite{48}, the use for staging and restaging\cite{49}, the standardized uptake values (commonly known as SUVs) and how they relate to lymph node status\cite{50}, the prognostic role of FDG-PET\cite{51} and the suitability for treatment planning\cite{52}; all these represent immensely exciting domains of breast cancer research, but would have confused the scope of the present study, namely the rates of DM.

In summary, the current review suggests a need for future prospective studies looking at subgroups of patients who would most likely benefit from PET scan before surgery-stage II B, poorly differentiated tumors, rare tumors with aggressive biology, such as invasive micropapillary carcinoma, and young age. These patients would most likely receive systemic therapy. Detection of DM could help in selecting the optimal sequence of therapies and the monitoring thereof. Incorporating biomarkers such as c-erbB2 and genetic arrays in those studies may further help the clinician to define the risk of DM at diagnosis for patients with early stage breast cancer.
Conclusion
In patients with clinical stage I breast cancer, the systematic use of 18FDG-PET/CT scan for staging is not cost effective because the yield of 18FDG-PET/CT-detected DM in clinical stage I is low. In young patients with stage I B triple-negative and/or poorly differentiated breast cancer, 18FDG-PET/CT scan identifies a substantial rate of DM and should therefore be considered for these patients. Finally, the role of 18FDG-PET for stage II breast cancer and for rare tumors with aggressive biology needs to be defined in future prospective studies.

ACKNOWLEDGMENTS
The authors would like to express their heartfelt gratitude to Carl Leak, for revising the language of this manuscript, to Jessica Malki, Olga Morgan, Brentwood Oftedal, Yeoshina Pillay and Andrew Westfall of the RSUM Oncology Society, Ross University School of Medicine, Dominica, West Indies for their enthusiastic interest and partaking in the discussion and the writing.

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**P- Reviewer:** Bilir C, Wang L, Wang SK  **S- Editor:** Ji FF  **L- Editor:** A  **E- Editor:** Lu YJ
