Letter to the Editor

PET/CT in Locally Advanced Breast Cancer: Time for a Guideline Change?

Re: Hyland CJ, Varghese F, Yau F, et al. Use of 18F-FDG PET/CT as an initial staging procedure for stage II–III breast cancer: a multicenter value analysis. *J Natl Compr Canc Netw* 2020;18(11):1510–1517.

We read with interest the article by Hyland et al,¹ in which 564 complete records of breast cancer patients with clinical stage II–III disease, who initiated screening for the I-SPY2 trial at 4 institutions, were reviewed to compare staging with FDG-PET/CT versus standard of care (SoC). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer recommend considering CT of the chest, abdomen ± pelvis, and bone scan in appropriate patients.² At this time, the NCCN Guidelines do not recommend FDG-PET/CT, but state that “FDG-PET/CT may ... be helpful in identifying unsuspected regional nodal disease and/or distant metastases when used in addition to standard imaging studies.” In the multicenter study by Hyland et al,¹ PET/CT reduced false-positive risk by half and decreased workup for incidental findings, allowing for earlier treatment start. PET/CT was cost-effective, and at one institution was shown to be cost-saving. The de novo metastatic disease rate was 4.6%. However, the authors offer no results by stage or tumor/node combination to help clinical decisions. In another recent study published in *JNCCN*,³ among 196 patients with breast cancer, the overall upstaging rate to stage IV based on findings of unsuspected distant metastases was 14% (n=27), including 0% for stage IIA, 13% for stage IIB (10/79), 22% for stage IIIA (9/41), 17% for stage

IIIB (5/30), and 37% for stage IIIC (3/8). PET/CT had comparable costs than SoC and had lower radiation dose exposure.³ In another recent retrospective study, PET/CT demonstrated distant disease in 4.9% of 303 patients with stage I or II breast cancer, including 0.8% in stage IIA and 9.8% in stage IIB breast cancer.⁴ In a prospective study of 254 patients with breast cancer, we detected distant metastases with PET/CT in 2.3% of patients with stage IIA disease, and in 10.7% with clinical stage IIB disease.⁵ PET/CT had similar performances whatever the breast cancer subtype. Other studies also showed that PET/CT reveals distant metastases in 10% to 15% of patients with stage IIB disease, whatever the breast cancer subtype.⁵ Nodal metastases outside Berg-I/II levels should also be taken into account, identified with PET/CT, with impact on management.^{5,6}

The 2 recent manuscripts in *JNCCN* add financial and radiation protection data to support the assertion that FDG-PET/CT should be used in patients with IIB–IIIC breast cancer. We hope this growing evidence will lead consensus guidelines to include FDG-PET/CT for the systemic staging of IIB–IIIC breast cancer at initial diagnosis.

David Groheux, MD, PhD^{a,t};
Elif Hindié, MD, PhD^b;
Marc Espié, MD^c; and
Gary A. Ulaner, MD, PhD^d

^aDepartment of Nuclear Medicine,
Saint-Louis Hospital,

Paris, France;

^bDepartment of Nuclear Medicine,
Bordeaux University Hospital,
Bordeaux, France;

^cBreast Diseases Unit,
Saint-Louis Hospital,
Paris, France; and

^dMolecular Imaging and Therapy,
Hoag Family Cancer Institute,
Newport Beach, California

[†]Email: dgroheux@yahoo.fr

doi: 10.6004/jnccn.2021.7050

References

- Hyland CJ, Varghese F, Yau C, et al. Use of 18F-FDG PET/CT as an initial staging procedure for stage II–III breast cancer: a multicenter value analysis. *J Natl Compr Canc Netw* 2020;18:1510–1517.
- Gradishar WJ, Moran MS, Abraham J, et al. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 4.2021. Accessed May 31, 2021. To view the most recent version, visit [NCCN.org](https://www.nccn.org)
- Ko H, Baghdadi Y, Love C, et al. Clinical utility of 18F-FDG PET/CT in staging localized breast cancer before initiating preoperative systemic therapy. *J Natl Compr Canc Netw* 2020;18:1240–1246.
- Srouf MK, Amersi F. Response to letter to the editor: 18FDG-PET/CT imaging in breast cancer patients with clinical stage IIB or higher. *Ann Surg Oncol* 2020;27:1710–1711.
- Groheux D, Hindié E, Delord M, et al. Prognostic impact of (18)FDG-PET-CT findings in clinical stage III and IIB breast cancer. *J Natl Cancer Inst* 2012;104:1879–1887.
- Ulaner GA. PET/CT for patients with breast cancer: where is the clinical impact? *AJR Am J Roentgenol* 2019;213:254–265.

Authors' Reply

To the Letter to the Editor by Groheux et al

The recent articles by Ko et al¹ and our group² contribute to the growing consensus that 18F-FDG PET/CT adds value to the care of locally advanced breast cancer. Retrospective and prospective evidence suggests that 18F-FDG PET/CT detects unsuspected axillary and distant metastases in a sizable proportion of patients, with detection rate increasing by stage.^{3–5} 18F-FDG PET/CT is both more sensitive and specific than conventional imaging (CT +

bone scan) in this patient population.^{2,5–7} Identification of distant metastatic disease directly affects management, potentially preventing costs, morbidity, and emotional burden associated with inappropriate treatments. In the ECOG-ACRIN E2108 trial, no survival benefit was observed in patients with de novo stage IV breast cancer randomized to surgery for locoregional control after a course of systemic therapy.⁸ Although some patients still opt to proceed

with surgery in the setting of stage IV disease, recognition of distant metastases may lead some to revise their surgical preferences. Furthermore, in known stage IV disease, oncologists may opt to refrain from recommending chemotherapy with the goal of cure and are more likely to recommend a hormone-based therapy regimen, particularly for older patients or those with minimal visceral disease. Conversely, data from the phase II SABR-COMET trial

suggest that stereotactic ablative radiotherapy in patients with solid tumors and 1 to 5 known metastatic sites improves overall survival.⁹ Although the number of patients with breast cancer in this study was small, the potential of “cure” in patients with oligometastatic disease has resonated, driving a rationale for the most sensitive imaging study to ascertain stage and sites of disease, not only at diagnosis but also along the trajectory of care.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer as well as other guidelines do not yet recommend ¹⁸F-FDG PET/CT for first-line imaging in locally advanced breast cancer.¹⁰ This is at least partly related to concerns regarding higher up-front cost of ¹⁸F-FDG PET/CT. As physicians, we have a duty to balance individual patient well-being with prudent stewardship of limited healthcare resources. For staging locally advanced breast cancer, there is mounting evidence that ¹⁸F-FDG PET/CT is not just diagnostically superior but also cost-effective. In the Ko et al¹ study, overall costs of ¹⁸F-FDG PET/CT and CT plus bone scan were comparable. In the Hyland et al² study, costs were comparable or in some cases less for ¹⁸F-FDG PET/CT, driven by decreased biopsies and follow-up imaging to resolve equivocal or suspicious findings on CT and/or bone scan. Neither study evaluated cost savings associated with avoidance of futile surgery and/or radiation in accurately upstaged patients, which may further

increase the cost-effectiveness of ¹⁸F-FDG PET/CT. Further study is needed to determine overall cost effectiveness of ¹⁸F-FDG PET/CT across different practice systems and patient populations. Additionally, we must determine the impact of more sensitive up-front staging on outcomes such as disease-specific and overall survival in patients with locally advanced breast cancer. Given the increasing evidence supporting the improved accuracy of ¹⁸F-FDG PET/CT, it is time to include this imaging modality in the guidance for metastatic workup for stage II and III breast cancer, given that it is the more patient-centered option.

Courtney Lawhn Heath, MD^a;
Laura J. Esserman, MD, MBA^a;
Robert R. Flavell, MD, PhD^a; and
Michelle E. Melisko, MD^{a,†}

^aUniversity of California,
San Francisco, California

[†]Email: mmelisko@medicine.ucsf.edu

doi: 10.6004/jnccn.2021.7080

References

1. Ko H, Baghdadi Y, Love C, Sparano JA. Clinical Utility of 18F-FDG PET/CT in staging localized breast cancer before initiating pre-operative systemic therapy. *J Natl Compr Canc Netw* 2020;18:1240–1246.
2. Hyland CJ, Varghese F, Yau C, et al. Use of 18F-FDG PET/CT as an initial staging procedure for stage II-III breast cancer: a multi-center value analysis. *J Natl Compr Canc Netw* 2020;18:1510–1517.
3. Caresia Aroztegui AP, Garcia Vicente AM, et al. 18F-FDG PET/CT in breast cancer: evidence-based recommendations in initial staging. *Tumour Biol* 2017;39:1010428317728285.
4. Han S, Choi JY. Impact of 18F-FDG PET, PET/CT, and PET/MRI on staging and management as an initial staging modality in breast cancer: a systematic review and meta-analysis. *Clin Nucl Med* 2021;46:271–282.
5. Hong S, Li J, Wang S. 18FDG PET-CT for diagnosis of distant metastases in breast cancer patients. A meta-analysis. *Surg Oncol* 2013;22:139–143.
6. Sun Z, Yi YL, Liu Y, et al. Comparison of whole-body PET/PET-CT and conventional imaging procedures for distant metastasis staging in patients with breast cancer: a meta-analysis. *Eur J Gynaecol Oncol* 2015;36:672–676.
7. Rong J, Wang S, Ding Q, et al. Comparison of 18 FDG PET-CT and bone scintigraphy for detection of bone metastases in breast cancer patients. A meta-analysis. *Surg Oncol* 2013;22:86–91.
8. Zhao FM, Solin LJ, Goldstein LJ, et al. A randomized phase III trial of systemic therapy plus early local therapy versus systemic therapy alone in women with de novo stage IV breast cancer: a trial of the ECOG-ACRIN Research Group (E2108) [abstract]. *J Clin Oncol* 2020;38(Suppl):Abstract LBA2.
9. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet* 2019;393:2051–2058.
10. Gradisher WJ, Moran MS, Abraham J, et al. NCCN Clinical Practice Guidelines In Oncology: Breast Cancer. Version 3.2021. Accessed May 1, 2021. To view the most recent version, visit NCCN.org

CALL FOR CORRESPONDENCE

JNCCN is committed to providing a forum to enhance collaboration between academic medicine and the community physician. We welcome comments about the NCCN Guidelines, articles published in the journal, or any other topic relating to cancer prevention, detection, treatment, supportive care, or survivorship. Please submit correspondence to www.editorialmanager.com/JNCCN.

Letters should be no more than 400 words, with no more than 5 references if included. NCCN reserves the right not to publish correspondence for any reason it deems appropriate. All letters are subject to editing and/or abridgment.