

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: PET SCANNING FOR BREAST CANCER

Approved 8/8/2013; reaffirmed 1/14/2016

This coverage guidance was created under HERC's 2013 coverage guidance process and does not include strength of recommendation, a GRADE-informed framework or coverage guidance development framework.

As a part of the coverage guidance monitoring process, the HERC decided on 1/14/2016 (see Appendix A) to reaffirm the existing coverage guidance and reconsider the need to update the topic during the regular two-year review cycle.

HERC COVERAGE GUIDANCE

PET scanning is not recommended for coverage in initial staging of breast cancer at low risk for metastasis (asymptomatic individuals with newly identified ductal carcinoma in situ, or clinical stage I or II disease).

PET scanning is not recommended for coverage as a modality to monitor response to treatment of breast cancer.

PET scanning is not recommended for coverage for surveillance testing for asymptomatic individuals who have been treated for breast cancer with curative intent.

RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows to translate the evidence review to a policy decision. Coverage guidance may be based on an evidence-based guideline developed by the Evidence-based Guideline Subcommittee or a health technology assessment developed by the Health Technology Assessment Subcommittee. In addition, coverage guidance may utilize an existing evidence report produced by one of HERC's trusted sources, generally within the last three years.

EVIDENCE SOURCES

Choosing Wisely®, the ABIM Foundation. (2012). Lists. Retrieved July 6, 2012, from http://choosingwisely.org/?page_id=13

HAYES, Inc. (2010). *Positron emission tomography (PET) and combined positron emission tomography-computed tomography (PET-CT) for breast cancer staging*. Lansdale, PA: HAYES, Inc.

National Collaborating Centre for Cancer (NCCC). (2009). *Advanced breast cancer: diagnosis and treatment – Evidence review*. Cardiff, Wales: National Collaborating Centre for Cancer. Retrieved May 23, 2012, from <http://guidance.nice.org.uk/index.jsp?action=download&o=44046>

Pennant, M., Takwoingi, Y., Pennant, L., Davenport, C., Fry-Smith, A., Eisinga, A., et al. (2010). A systematic review of positron emission tomography (PET) and positron emission tomography/computed tomography (PET/CT) for the diagnosis of breast cancer recurrence. *Health Technology Assessment, 14*(50).

Schnipper, L.E., Smith, T.J., Raghavan, D., Blayney, D.W., Ganz, P.A., Mulvey, T.M., et al. (2012). American Society of Clinical Oncology identified five key opportunities to improve care and reduce costs: The top five list for oncology. *Journal of Clinical Oncology, 30*(14), 1715-1724.

The summary of evidence in this document is derived directly from these evidence sources, and portions are extracted verbatim.

SUMMARY OF EVIDENCE

Clinical Background

Breast cancer affects 1 in 13 women in their lifetime. Treatment options have developed significantly over the past decade and have had an impact on survival. Initial staging and the diagnosis of BC recurrence is important to allow appropriate treatment. Positron emission tomography (PET) and positron emission tomography/computed tomography (PET/CT) are technologies that have application in the detection and management of cancer. The adoption of PET or PET/CT depends not only on their diagnostic accuracy but also on their comparative advantage over existing diagnostic approaches.

Choosing Wisely® Campaign 2012

In 2010, Howard Brody, MD, PhD, Director of the Institute for Medical Humanities and a family medicine professor at the University of Texas, challenged medical specialty societies to identify five tests and treatments that are commonly performed in their respective fields despite a lack of evidence that they provide meaningful benefit to major

categories of patients. Dr. Brody's commentary, "Medicine's Ethical Responsibility for Health Care Reform—The Top Five List," was published in the *New England Journal of Medicine*, and spawned the American Board of Internal Medicine (ABIM) Foundation's *Choosing Wisely*[®] campaign. *Choosing Wisely*[®] is part of a multi-year effort of the ABIM Foundation to help physicians be better stewards of finite health care resources. Originally conceived and piloted by the [National Physicians Alliance](#) through a [Putting the Charter into Practice grant](#), nine medical specialty organizations, along with Consumer Reports, have identified five tests or procedures commonly used in their field, whose necessity should be questioned and discussed. Each participating organization was free to determine how to create its own list, provided that it used a clear methodology and adhered to the following set of shared guidelines:

- Each item should be within the specialty's purview and control.
- The tests and/or interventions should be used frequently and/or carry a significant cost.
- Each recommendation should be supported by generally accepted evidence.
- The selection process should be thoroughly documented and publicly available on request.

One of the organizations that chose to participate in the *Choosing Wisely*[®] campaign is the American Society of Clinical Oncologists (ASCO). The Cost of Care Task Force of ASCO worked for several months to identify a list for ASCO to consider as its Top Five, first by suggesting a number of practices they believed were overused, then by performing a literature search to ensure that the items identified were supported by available evidence.

Two of the recommendations on ASCO's top five list pertain to PET scanning, and are presented below, along with clinical rationale. Citations supporting these recommendations are provided in the text with superscripted numerals. Full references can be found at the end of this document.

Don't perform PET, CT, and radionuclide bone scans in the staging of early breast cancer at low risk for metastasis.

Early-stage breast cancer (including ductal carcinoma in situ, and clinical stages I and II) is a potentially curable disease and a common problem faced by surgical, medical, and radiation oncologists.¹ Curative treatment of localized breast cancer can be accomplished by excision of the primary tumor followed with radiation therapy, or by mastectomy. Depending on a variety of factors, including the biomarkers associated with the primary cancer, systemic treatment—including hormonal therapy, chemotherapy, and biologic therapy—may be appropriate. Because the staging determination is critical to appropriate application of surgical, radiation, and systemic

treatment with their associated short-term and long-term toxicities, there is great pressure to accurately assess disease stage in each patient.

Clinical staging (based on history and a physical examination by an oncology-trained physician), combined with serum tests of liver function and alkaline phosphatase, is the standard method to separate early breast cancer from metastatic or locally advanced breast cancer. Patients with locally advanced breast cancer (e.g., stage III) have a higher risk of occult metastatic disease, which may be discovered by FDG PET or PET/CT scanning, and use of these tests in this setting is appropriate.

The available evidence-based guideline does not recommend FDG PET or CT scanning for patients with stages I, IIa, and IIb breast cancer who are asymptomatic and have no findings on routine clinical and pathologic staging to suggest a more advanced stage.² The guideline is based on information available from retrospective studies of imaging in early-stage breast cancer. These studies show that the low incidence of occult liver and bone metastases (< 6%) is mostly in patients with stage III cancer, not in those with stages I and II,^{3,4} and many of the findings are falsely positive (i.e., not due to metastatic cancer).⁵ FDG PET is inferior to physical examination and sentinel lymph node biopsy for detecting axillary lymph node metastases.^{6,7} In patients with large, stage III tumors or inflammatory breast cancer, FDG PET detects occult metastases in 10% to 21% of patients.⁸⁻¹²

In addition to excess cost, unwarranted testing leads to needless exposure of the patient to dangers of invasive procedures stimulated by false-positive results, the inherent anxiety and uncertainty associated with a false positive result, and unjustified exposure to ionizing radiation in women at low risk of dying as a result of breast cancer.¹³

Don't perform surveillance testing (biomarkers) or imaging (PET, CT, and radionuclide bone scans) for asymptomatic individuals who have been treated for breast cancer with curative intent.

Surveillance testing with serum tumor markers or imaging with PET, CT, and radionuclide bone scans has been shown to have clinical value for certain cancers (e.g., colorectal). However for breast cancer that has been treated with curative intent, several studies have shown there is no benefit from routine imaging or serial measurement of serum tumor markers in asymptomatic patients. False-positive tests can lead to harm through unnecessary invasive procedures, overtreatment, and misdiagnosis.

The majority of patients with breast cancer diagnosed today present with early-stage, node-negative disease that is found on screening mammography.¹ As a result of earlier diagnosis and the efficacy of adjuvant therapies (chemotherapy, radiation, endocrine therapy), most of these women have a normal life expectancy and a low risk for

recurrence. Surveillance for breast cancer recurrence in this setting is particularly low yield given the low prevalence of recurrence. For a surveillance or screening test to be considered useful, it must have high sensitivity and specificity, as well as a significant positive predictive value, the latter being highly dependent on the prevalence of the condition. Furthermore, screening tests need to add value through detecting early-stage disease for which treatment will improve survival outcomes. To date, there is no evidence from randomized trials that earlier detection of asymptomatic breast cancer recurrence (outside of the breast, as a local recurrence, or new primary) improves survival outcomes.^{14,15,16-18} In addition, these studies suggest that most breast cancer recurrence is detected through clinical symptoms and not through screening. Thus, making patients aware of the potential symptoms of a breast cancer recurrence (e.g., pain, new lumps, dyspnea) is an important strategy in breast cancer surveillance.

Other imaging strategies such as standard chest radiograph, bone scans, and abdominal ultrasound did not change survival outcomes in the two randomized trials conducted in the 1990s,^{17,18} and thus are not recommended for routine surveillance. Chest and abdominal CT scans or whole-body PET scans have not been evaluated as surveillance strategies for follow-up of early-stage breast cancer, even though they may be of value for the diagnostic evaluation of clinically evident recurrent breast cancer.¹⁴ Given the low prevalence of distant recurrence in early-stage breast cancer, and the high likelihood of false-positive findings and/or incidental findings that will lead to further testing, there is no evidence to support the use of these imaging strategies.^{14,16}

Evidence Review

The evidence sources presented below pertain to the diagnostic characteristics of PET scanning compared to other diagnostic modalities for various stages of breast cancer. None of the literature identified pertains to whether any imaging is indicated in each clinical situation.

Staging

Hayes 2010

Detection of Axillary Lymph Node Metastasis: Twelve of the studies compared the accuracy of the interventions to that of axillary lymph node dissection alone or in combination with sentinel lymph node biopsy. The sensitivity of PET in detecting axillary lymph node metastasis was reported as poor (27% to 61%) in five studies, moderate (68% and 80%) in two studies, and high (90.1% and 94.4%) in two studies. The corresponding specificity of PET was reported as moderate (67% to 89%) in four studies and high (95 to 100%) in five studies. The sensitivity of PET/CT was moderate (70% and 80%) in two studies and poor (48.5%) in one study. The specificity was moderate (84%) in one study and high (100%) in a second study. One study did not

report on specificity, and none of the studies directly compared the performance of PET with PET/CT; therefore, there is no evidence that assesses the incremental impact that PET/CT has on detecting metastasis. Direct comparison was made between PET and only one other imaging technique. Technetium 99 methoxyisobutylisonitrile (^{99m}Tc -MIBI) SPECT with or without planar scintigraphy demonstrated a slightly lower sensitivity of 38% (compared with 50%) in detecting axillary lymph node metastasis. Specificity was equivalent to that of PET/CT.

Detection of Distant Metastasis: Four studies assessed the performance of ^{18}F -FDG PET relative to conventional imaging or biopsy in identifying distant metastasis. In the three studies that reported the results per patient, sensitivity was in the range from 80% to 100% and specificity was 83% to 96.7%. The study population sizes ranged from 40 to 119. Two of the studies were retrospective. In the fourth study, in which the results were reported per lesion, PET sensitivity was 95.2% and specificity was 90.9% in 40 patients. The analysis in this study was also retrospective. Two of the studies compared the performance of ^{18}F -FDG PET with technetium-99m-labeled hydromethylene diphosphonate (^{99m}Tc -HMDP). In one study, ^{99m}Tc -HMDP was less sensitive but more specific than PET, while in the second study, ^{99m}Tc -HMDP was less accurate than PET. In a third study, ^{99m}Tc -MDP was as sensitive as ^{18}F -FDG PET but significantly less specific in a population of 40 patients. The fourth study reported that ^{18}F -FDG PET in 119 patients was more sensitive and less specific than conventional imaging in 116 patients.

Surveillance/Detection of Recurrence

[NCCC 2009](#)

Two systematic reviews and 15 small comparative studies or case series formed the evidence base for the topic on imaging to determine disease extent. Other than the reviews, papers were generally of poor to medium quality, and many were retrospective studies. Magnetic resonance imaging (MRI) and FDG-PET were equal to or better than scintigraphy in visualizing bone metastases, other than osteoblastic lesions, but whole body MRI was better than FDG-PET at detecting distant metastases, particularly in abdominal organs, brain, and bone. Magnetic resonance imaging also detected previously unidentified metastases, including those that were non-skeletal, and in one study, the treatment plan was changed accordingly in ~43% of patients. Computed tomography had a high diagnostic value in detecting local breast cancer recurrence and, when the field was extended to include the pelvis, also had a higher diagnostic accuracy in detecting bone metastases than scintigraphy.

[Pennant 2010](#)

In studies where direct comparisons of PET were made to conventional imaging tests (X-rays, CT, ultrasound and bone scintigraphy) and test performance was assessed

based on individual patients (rather than lesions), PET had significantly higher sensitivity (89% vs. 79%) and significantly higher specificity (93% vs. 83%). Test performance did not appear to vary according to the type of conventional imaging test that was compared with PET. Indirect comparisons gave similar findings. For studies that assessed test accuracy based on lesions, no significant differences in sensitivity or specificity between PET and conventional imaging tests were observed.

In studies where direct comparisons of PET/CT were made to CT (no studies of PET/CT and other imaging tests were identified), PET/CT had significantly higher sensitivity (95% vs. 80%), but the increase in specificity was not significant. Indirect comparisons gave the same findings.

For studies where test performance was assessed based on individual patients, three studies compared PET with different types of MRI technology. In each of these studies, there were no significant differences in the sensitivity or specificity of PET compared with MRI. One study compared PET/CT and MRI on a lesion basis, and there were no significant differences in sensitivity or specificity for PET/CT compared with MRI.

In the analysis of studies directly comparing PET/CT and PET, PET/CT had significantly higher sensitivity (96% vs. 85%), but the increase in specificity was not significant compared with PET (89% vs. 82%). The same pattern of results was observed for the indirect comparison of all PET/CT and PET studies. For studies that assessed test accuracy based on lesions, indirect comparison of PET/CT and PET showed no significant differences in sensitivity or specificity between PET/CT and PET.

Changes in patient management in study participants ranged from 11% to 74% (median 27%). These changes included initiation and avoidance of medical treatment such as hormone therapy and chemotherapy. In the three studies where only changes in management directly due to PET or PET/CT were considered (patients were not correctly diagnosed by conventional imaging techniques), estimates ranged from 11% to 25%.

In subgroup analysis, the accuracy of PET did not appear to be related to the location of disease or to whether PET was conducted with or without knowledge of previous clinical history and imaging studies. Characteristics of patient populations varied in many respects, and it was not possible to draw definite conclusions about patient characteristics that may have an impact on test accuracy.

Monitoring response to treatment

[NCCC 2009](#)

The evidence available to address this question is limited to six small (n=18 to 274) case series. Reviewed imaging modalities include MRI (comparing fat-suppressed-long-

echo-time-inversion images to T1-weighted-sequence images), plain radiography, FDG-PET and fluoroestradiol-PET. The paucity and poor quality of studies prevents meaningful analysis of efficacy.

Overall Summary

The *Choosing Wisely*[®] campaign recommends that PET scanning NOT be performed in early stage (DCIS, stage I, IIa and IIb) breast cancer because there is no evidence demonstrating a clinical benefit, and unnecessary imaging can lead to harm through unnecessary invasive procedures, over-treatment, and unnecessary radiation exposure. It also recommends that PET scanning NOT be performed for surveillance of asymptomatic patients who have been treated for breast cancer with curative intent.

For initial staging, compared to axillary lymph node dissection alone or in combination with sentinel lymph node biopsy, the sensitivity of PET in detecting axillary lymph node metastasis was reported as widely variable, ranging from 27% to 94%. The corresponding specificity of PET ranged from 67% to 100%. Assessment of the accuracy of PET/CT was limited to three trials, which reported sensitivity ranging from 48% to 80%, while the specificity ranged from 84% to 100%. For detection of distant metastases at the time of initial staging, accuracy results for PET relative to conventional imaging or biopsy were mixed, with sensitivity ranging from 80% to 100% and specificity from 83% to 96.7%.

For detection of recurrence, PET had significantly higher sensitivity and specificity compared to conventional imaging tests. Positron emission tomography/CT had a higher sensitivity than CT, no significant difference in specificity. Magnetic resonance imaging and PET have similar accuracy, and were equal to or better than scintigraphy in visualizing bone metastases, other than osteoblastic lesions.

For monitoring response to treatment, the evidence is insufficient to draw conclusions.

COMMITTEE DELIBERATIONS-HTAS

At its November 26, 2012 meeting of HTAS, a previous draft of the coverage guidance contained the words “routine” and “routinely” to allow for exceptions in nonroutine cases for monitoring treatment response or surveillance testing in individuals previously treated. After discussion, the subcommittee elected to remove the words, “routine” and “routinely” as they create ambiguity. The subcommittee did not find evidence that PET scans would be appropriate for these indications even in nonroutine circumstances, such as monitoring response to treatment of a cancer originally detected by PET scan. The subcommittee made no significant changes to the coverage guidance during the February 25, 2013 HTAS meeting.

COMMITTEE DELIBERATIONS-VbBS

PROCEDURE

PET scanning

DIAGNOSES

Cancer of the breast

APPLICABLE CODES

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
174	Malignant neoplasm of female breast
233.0	Carcinoma in situ of breast
ICD-9 Volume 3 (Procedure Codes)	
92.18	Radioisotope scan; total body
92.19	Radioisotope scan; other sites
CPT Codes	
78811-3	PET imaging
78814-6	PET/CT imaging
79005-99	Systemic radiopharmaceutical therapy
HCPCS Codes	
None	

Note: Inclusion on this list does not guarantee coverage

ASCO References

1. American Cancer Society: Breast cancer facts and figures.
<http://www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-030975.pdf>
2. Carlson RW, Allred DC, Anderson BO, et al: Invasive breast cancer. J Natl Compr Canc Netw 9:136-222, 2011
3. Barry MC, Thornton F, Murphy M, et al: The value of metastatic screening in early primary breast cancer. Ir J Med Sci 168:248-250, 1999
4. 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 16:263-266, 2005
5. Norum J, Andreassen T: Screening for metastatic disease in newly diagnosed breast cancer patients. What is cost-effective? Anticancer Res 20:2193-2196, 2000
6. Wahl RL, Siegel BA, Coleman RE, et al: Prospective multicenter study of axillary nodal staging by positron emission tomography in breast cancer: A report of the staging breast cancer with PET Study Group. J Clin Oncol 22:277-285, 2004
7. Kumar R, Zhuang H, Schnall M, et al: FDG PET positive lymph nodes are highly predictive of metastasis in breast cancer. Nucl Med Commun 27:231-236, 2006

8. van der Hoeven JJ, Krak NC, Hoekstra OS, et al: 18F-2-fluoro-2-deoxy-d-glucose positron emission tomography in staging of locally advanced breast cancer. *J Clin Oncol* 22:1253-1259, 2004
9. Mahner S, Schirrmacher S, Brenner W, et al: Comparison between positron emission tomography using 2-[fluorine-18]fluoro-2-deoxy-D-glucose, conventional imaging and computed tomography for staging of breast cancer. *Ann Oncol* 19:1249-1254, 2008
10. Fuster D, Duch J, Paredes P, et al: Preoperative staging of large primary breast cancer with [18F]fluorodeoxyglucose positron emission tomography/computed tomography compared with conventional imaging procedures. *J Clin Oncol* 26:4746-4751, 2008
11. Groheux D, Moretti JL, Baillet G, et al: Effect of (18)F-FDG PET/CT imaging in patients with clinical Stage II and III breast cancer. *Int J Radiat Oncol Biol Phys* 71:695-704, 2008
12. Carkaci S, Macapinlac HA, Cristofanilli M, et al: Retrospective study of 18F-FDG PET/CT in the diagnosis of inflammatory breast cancer: Preliminary data. *J Nucl Med* 50:231-238, 2009
13. Huang B, Law MW, Khong PL: Whole-body PET/CT scanning: Estimation of radiation dose and cancer risk. *Radiology* 251:166-174, 2009
14. Khatcheressian JL, Wolff AC, Smith TJ, et al: American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guideline in the adjuvant setting. *J Clin Oncol* 24:5091-5097, 2006
15. Harris L, Fritsche H, Mennel R, et al: American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. *J Clin Oncol* 25:5287-5312, 2007
16. Rojas MP, Telaro E, Russo A, et al: Follow-up strategies for women treated for early breast cancer. *Cochrane Database Syst Rev* 1:CD001768, 2005
17. Rosselli Del Turco M, Palli D, Cariddi A, et al: Intensive diagnostic follow-up after treatment of primary breast cancer: A randomized trial—National Research Council Project on Breast Cancer followup. *JAMA* 271:1593-1597, 1994
18. Liberati A: The GIVIO trial on the impact of follow-up care on survival and quality of life in breast cancer patients: Interdisciplinary Group for Cancer Care Evaluation. *Ann Oncol* 6:41-46, 1995 (suppl 2)

Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

The Center is not engaged in rendering any clinical, legal, business or other professional advice. The statements in this document do not represent official policy positions of the Center. Researchers involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

Appendix A: 2015 Rescanning Summary

HERC decision (1/14/2016): Reaffirm the existing coverage guidance and reconsider the need to update the topic during the regular two-year review cycle.

Bottom Line: While new evidence may offer refined estimates of the diagnostic performance of PET, there remains a paucity of data regarding its effects on treatment plans or clinical outcomes.

Coverage Recommendation (Box Language)

PET scanning is not recommended for coverage in initial staging of breast cancer at low risk for metastasis (asymptomatic individuals with newly identified ductal carcinoma in situ, or clinical stage I or II disease).

PET scanning is not recommended for coverage as a modality to monitor response to treatment of breast cancer.

PET scanning is not recommended for coverage for surveillance testing for asymptomatic individuals who have been treated for breast cancer with curative intent.

Scope Statement

Population description	Adults with early stage breast cancer (DCIS, stage I, or stage II) or who have been treated for breast cancer with curative intent <i>Population scoping notes: None</i>
Intervention(s)	PET CT for initial staging, surveillance, or monitoring response to treatment <i>Intervention exclusions: None</i>
Comparator(s)	Usual care (including axillary lymph node dissection [with or without sentinel lymph node biopsy], CT and radionuclide scintigraphy), MRI
Outcome(s) (up to five)	Critical: All-cause mortality, cancer-specific mortality Important: Progression-free survival, false positive tests, quality of life <i>Considered but not selected for GRADE table: None</i>

Key questions	<ol style="list-style-type: none"> 1. What is the comparative effectiveness of PET CT in early stage breast cancer or breast cancer treated with curative intent in improving patient important outcomes for staging, monitoring response, or surveillance? 2. What are the harms (including false positive tests, radiation exposure) of PET in early stage breast cancer or breast cancer treated with curative intent? <p>Contextual Questions</p> <ol style="list-style-type: none"> 1. How often do the results of PET CT after breast cancer diagnosis lead to changes in the surgical or non-surgical treatment plan?
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Original Evidence Sources

Choosing Wisely®, the ABIM Foundation. (2012). Lists. Retrieved from http://choosingwisely.org/?page_id=13

HAYES, Inc. (2010). *Positron emission tomography (PET) and combined positron emission tomography-computed tomography (PET-CT) for breast cancer staging*. Lansdale, PA: HAYES, Inc.

National Collaborating Centre for Cancer (NCCC). (2009). *Advanced breast cancer: diagnosis and treatment – Evidence review*. Cardiff, Wales: National Collaborating Centre for Cancer. Retrieved from <http://guidance.nice.org.uk/index.jsp?action=download&o=44046>

Pennant, M., Takwoingi, Y., Pennant, L., Davenport, C., Fry-Smith, A., Eisinga, A., ... Hyde, C. (2010). A systematic review of positron emission tomography (PET) and positron emission tomography/computed tomography (PET/CT) for the diagnosis of breast cancer recurrence. *Health Technology Assessment*, 14(50).

Schnipper, L. E., Smith, T. J., Raghavan, D., Blayney, D. W., Ganz, P. A., ... Wollins, D. S. (2012). American Society of Clinical Oncology identified five key opportunities to improve care and reduce costs: The top five list for oncology. *Journal of Clinical Oncology*, 30(14), 1715-1724.

Scanning Results

1. Annunziata, S., Caldarella, C., & Treglia, G. (2014). Cost-effectiveness of Fluorine-18-Fluorodeoxyglucose positron emission tomography in tumours other than lung cancer: a systematic review. *World Journal of Radiology*, 6(3): 48-55. Retrieved from <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3986420/>

Citation 1 is a SR of cost-effectiveness studies of PET for cancers other than lung cancers. It includes 2 studies on the cost-effectiveness of PET for breast cancer, though these studies were done in Canada and the United Kingdom. In the Canadian study, PET was found to be cost-saving compared with axillary LND in newly diagnosed early stage breast cancer. In the UK study, a strategy of initial PET scanning dominated initial sentinel lymph node biopsy for new diagnoses of early stage breast cancer. However, these economic analyses may be too indirect to influence new coverage guidance.

2. Auguste P, Barton P, Hyde C, Roberts T. E. An economic evaluation of positron emission tomography (PET) and positron emission tomography/computed tomography (PET/CT) for the diagnosis of breast cancer recurrence. *Health Technol Assess* 2011;15(18). DOI: 10.3310/hta15180.

Citation 2 is an economic evaluation of PET for the diagnosis of recurrent breast cancer. The perspective was that of the British NHS. The incremental cost effectiveness ratio for PET was 31,000 GBP per QALY. This economic analysis would probably be too indirect to influence new coverage guidance.

3. Brennan, M. E. & Houssami, N. (2012). Evaluation of the evidence on staging imaging for detection of asymptomatic distant metastases in newly diagnosed breast cancer. *Breast*, 21(2), 112-123. DOI: 10.1016/j.breast.2011.10.005.

Citation 3 is a SR of 22 studies examining various modalities for the detection of asymptomatic distant metastases in newly diagnosed breast cancer. While PET has very good operating characteristics, the authors note that there is a low prevalence of distant metastatic disease in newly diagnosed early stage breast cancer (median prevalence of 0.2% to 1.2%) and that there is likely a selection bias in the literature they reviewed.

4. Bruening, W., Uhl, S., Fontanarosa, J., Reston, J., Treadwell, J., & Schoelles, K. (2012). Noninvasive diagnostic tests for breast abnormalities: Update of a 2006 review. Comparative Effectiveness Review No. 47. (Prepared by the ECRI Institute Evidence-based Practice Center under Contract No. 290-02-0019.) AHRQ Publication No. 12-EHC014-EF. Rockville, MD: Agency for Healthcare Research and Quality; February 2012. Retrieved from www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Citation 4 is an AHRQ review of various non-invasive imaging modalities for evaluation of abnormalities identified on routine screening. Based on 7 studies of PET, the summary sensitivity and specificity were 83% and 74% respectively. The authors conclude that the use of PET in this circumstance would not generally change management unless the pre-test probability of breast cancer was less than 5%. Furthermore, B-mode grayscale ultrasound and MRI appear to be more accurate than PET.

5. Clark, E. E. (2011). Positron emission tomography (PET) scanning in malignancy. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University. Retrieved from https://www.medclearinghouse.org/index.cfm?fuseaction=file.secure&loc=5&file=/topicfile_478.pdf.

Citation 5 is a MED report on PET for malignancy. With regard to its use in breast cancer, the report concludes that “PET is insufficiently accurate to be used instead of surgery for detection of cancer in breast masses or for axillary lymph node staging. MRI appears to be more accurate than PET for detection of recurrence or distant metastases. PET may be useful for identifying patients with advanced cancer who are or are not responding to treatment.”

6. Cooper, K. L., Meng, Y., Harnan, S., Ward, S. E., Fitzgerald, P., Papaioannou, D.,..., & Lorenz, E. (2011). Positron emission tomography (PET) and magnetic resonance imaging (MRI) for the assessment of axillary lymph node metastases in early breast cancer: Systematic review and economic evaluation. *Health Technology Assessment*, 15(4). DOI: 10.3310/hta15040.

Citation 6 is a SR and economic evaluation of PET, MRI, and various lymph node sampling techniques for the diagnosis of axillary lymph node metastases. In 26 included studies of PET, the summary sensitivity and specificity of PET were 63% and 94% respectively. PET performance was diminished for detection of small axillary metastases. In the cost-effectiveness analysis, MRI was the dominant strategy, though this UK economic analysis may be too indirect to influence new coverage guidance.

7. Deng, S. M., Zhang, W., Zhang, B., & Wu, Y. W. (2014). Assessment of tumor response to chemotherapy in patients with breast cancer using (18)F-FLT: a meta-analysis. *Chinese Journal of Cancer Research*, 26(5): 517-524. Retrieved from <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4220254/>

Citation 7 is a MA of 4 studies examining the use of PET for assessing response to chemotherapy for patients with breast cancer. The reference standard was histopathologic, clinical, or radiologic follow-up at 6 months. The summary sensitivity and specificity of PET for assessing response to chemotherapy were 77% and 68%

respectively. The study did not assess clinical outcomes or changes to treatment plans as a result of PET.

8. Gold, L. S., Lee, C. I., Devine, B., Nelson, H., Chou, R., Ramsey, S., & Sullivan, S. D. (2014). Imaging techniques for treatment evaluation for metastatic breast cancer [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014 Oct. (Technical Briefs, No. 17.) Retrieved from: <http://www.ncbi.nlm.nih.gov/books/NBK253155/>

Citation 8 is an AHRQ review of imaging modalities to assess response to treatment for patients with metastatic breast cancer. The authors conclude that “while some early evidence suggests that the metabolic response assessed by FDG-PET/CT after initial cycles of chemotherapy may be predictive of response to treatment among metastatic breast cancer patients, more rigorous research is needed before definitive conclusions can be reached.”

9. Hong, S., Li, J., & Wang, S. (2013). FDG PET-CT for diagnosis of distant metastases in breast cancer patients: a meta-analysis. *Surgical Oncology*, 22(2): 139-143. doi:10.1016/j.suronc.2013.03.001.

Citation 9 is a MA of 8 studies of PET for evaluation of distant metastatic disease in patients with breast cancer. The summary sensitivity and specificity of PET were 97% and 95% respectively. Changes in treatment plan or clinical outcomes were not reported.

10. MacDonald, S. M., Haffty, B. G., Harris, E. E., Arthur, D. W. , Bailey, L., Bellon, J. R., & Moran M. S. (2011). ACR Appropriateness Criteria® locally advanced breast cancer. [online publication]. Reston (VA): American College of Radiology (ACR). Retrieved from <http://www.guideline.gov/content.aspx?id=32632>

Citation 10 is ACR Appropriateness Criteria for various imaging modalities in patients with locally advanced breast cancer. The very specific scenarios used in this report would likely not be generalizable to an updated coverage guidance.

11. Mghanga, F. P., Lan, X., Bakari, K. H., Li C., & Zhang Y. (2013). Fluorine-18 fluorodeoxyglucose positron emission tomography-computed tomography in monitoring the response of breast cancer to neoadjuvant chemotherapy: a meta-analysis. *Clinical Breast Cancer*, 13(4): 271-279. DOI: 10.1016/j.clbc.2013.02.003.

Citation 11 is a SR and MA of 15 studies of PET for assessing the response to neoadjuvant chemotherapy. The summary sensitivity and specificity of PET for

distinguishing responders from non-responders were 80% and 79% respectively. Changes in treatment plan or clinical outcomes were not reported.

12. Moy, L., Newell, M. S., Bailey, L., Barke, L. D., Carkaci, S., D'Orsi, C., ... Mahoney M. C. (2014). ACR Appropriateness Criteria® stage I breast cancer: initial workup and surveillance for local recurrence and distant metastases in asymptomatic women [online publication]. Reston (VA): American College of Radiology (ACR). Retrieved from <http://www.guideline.gov/content.aspx?id=48278>

Citation 12 is ACR Appropriateness Criteria for various imaging modalities in the initial work-up or surveillance for asymptomatic local recurrence or distant metastases in patients with stage I breast cancer. For all proposed indications, PET receives a rating of 1 or 2 which is “usually not appropriate.”

13. Pan, L., Han, Y., Sun, X., Liu, J., & Gang, H. (2010). FDG-PET and other imaging modalities for the evaluation of breast cancer recurrence and metastases: a meta-analysis. *Journal of Cancer Research and Clinical Oncology*, 136(7): 1007-1022. DOI: 10.1007/s00432-009-0746-6.

Citation 13 is a SR and MA of 42 studies of imaging modalities for evaluation of breast cancer recurrence or metastases. The summary sensitivity and specificity of PET were 95% and 86% respectively. MRI was the only imaging modality with better operating characteristics. Changes in treatment plan or clinical outcomes were not reported.

14. Wang, Y., Zhang, C., Liu, J., & Huang, G. (2012). Is 18F-FDG PET accurate to predict neoadjuvant therapy response in breast cancer? A meta-analysis. *Breast Cancer Research and Treatment*, 131(2): 357-369. DOI: 10.1007/s10549-011-1780-z.

Citation 14 is a SR and MA of 19 studies examining the use of PET for evaluation of response to neoadjuvant chemotherapy. Compared to a reference standard of histopathologic response in primary breast cancers, the summary sensitivity and specificity of PET were 84% and 66% respectively. Changes in treatment plan or clinical outcomes were not reported.

Methods

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, technology assessments, and clinical practice guidelines using the terms “coronary computed tomography” and “coronary CT angiography.” Searches of core sources were limited to citations published after 2011.

The core sources searched included:

- Agency for Healthcare Research and Quality (AHRQ)
- Blue Cross/Blue Shield Health Technology Assessment (HTA) program
- BMJ Clinical Evidence*
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Cochrane Library (Wiley Interscience)
- Hayes, Inc.
- Medicaid Evidence-based Decisions Project (MED)
- National Institute for Health and Care Excellence (NICE)
- Tufts Cost-effectiveness Analysis Registry
- Veterans Administration Evidence-based Synthesis Program (ESP)
- Washington State Health Technology Assessment Program

A MEDLINE® (Ovid) search was conducted to identify systematic reviews, meta-analyses, and technology assessments published after the search dates of original evidence sources. The search was limited to publications in English published after 2011.

Searches for clinical practice guidelines were limited to those published since 2012. A search for relevant clinical practice guidelines was also conducted, using the following sources:

- Australian Government National Health and Medical Research Council (NHMRC)
- Centers for Disease Control and Prevention (CDC) – Community Preventive Services
- Institute for Clinical Systems Improvement (ICSI)
- National Guidelines Clearinghouse
- New Zealand Guidelines Group
- NICE
- Scottish Intercollegiate Guidelines Network (SIGN)
- United States Preventive Services Task Force (USPSTF)
- Veterans Administration/Department of Defense (VA/DOD)

Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English, did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessment, or clinical practice guidelines.

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