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Review

Comparative effectiveness of imaging modalities to determine metastatic breast cancer treatment response

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ABSTRACT

We performed a systematic review to address the comparative effectiveness of different imaging modalities in evaluating treatment response among metastatic breast cancer patients. We searched seven multidisciplinary electronic databases for relevant publications (January 2003–December 2013) and performed dual abstraction of details and results for all clinical studies that involved stage IV breast cancer patients and evaluated imaging for detecting treatment response. Among 159 citations reviewed, 17 single-institution, non-randomized, observational studies met our inclusion criteria. Several studies demonstrate that changes in PET/CT standard uptake values are associated with changes in tumor volume as determined by bone scan, MRI, and/or CT. However, no studies evaluated comparative test performance between modalities or determined relationships between imaging findings and subsequent clinical decisions. Evidence for imaging's effectiveness in determining treatment response among metastatic breast cancer patients is limited. More rigorous research is needed to address imaging's value in this patient population.

Introduction

Initial presentation with metastatic breast cancer is uncommon, occurring in only approximately 5% of breast cancer cases [1]. However, up to 50% of breast cancer patients may eventually develop metastatic disease [2]. Breast cancer most commonly metastasizes to the bones, lungs, liver, or brain, and metastatic disease is associated with a 5-year relative survival rate of 23% [3]. While metastatic breast cancer is considered incurable, systemic treatments including chemotherapy can help alleviate symptoms, delay tumor growth and spread, and improve disease-free survival [4–6].

Identifying metastatic breast cancer patients who do not respond to therapy early in the course of systemic treatment can help avoid unnecessary drug-related toxicities with potential improvements on quality of life and clinical outcomes [7]. Treatment response of metastatic lesions is currently assessed by serial medical imaging exams; however, imaging protocols are hampered by the fact that different modalities better depict metastases located in different anatomic areas. Depending on the organ(s) involved, nuclear medicine bone scan, CT (computed tomography), and/or MRI (magnetic resonance imaging) may be used to follow the size of distant breast cancer metastases over time to determine treatment response [8–10].

The evaluation of treatment response by conventional imaging is also limited because changes in tumor size may not become evident by imaging until after several cycles of chemotherapy. A relatively recent imaging advance for treatment-related response among breast cancer patients is positron emission tomography

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(PET), a whole-body imaging modality that allows functional assessment of tumor metabolism prior to anatomic size changes [11–13]. Since 2006, all PET scanners purchased in the United States have been combined with conventional CT scanners [14]. The addition of CT to PET has improved the accuracy of tumor status measurement based on better anatomic correlation [15]. Thus, PET/CT allows the evaluation of treatment response on a lesion-by-lesion basis regardless of the organ systems involved, detecting early metabolic changes to tumors using a single, whole-body, functional imaging exam [16]. With PET/CT, treatment response assessment typically involves measuring the change in maximum standard uptake value, with relative decreases in value suggestive of response to therapy.

Multiple studies have demonstrated the utility of PET/CT for evaluating treatment response in patients with locally advanced breast cancer [17–21]. Furthermore, assessment of treatment response of primary breast tumors by PET/CT has been validated in the neoadjuvant setting, where early changes in standardized uptake values correlates highly with histopathological response [22,23]. However, there has been less reported on the utility of PET/CT, as well as the utility of conventional imaging, for predicting response early in the treatment course among metastatic breast cancer patients. As reflected in guidelines from the National Comprehensive Cancer Network and the National Institute for Health and Clinical Excellence, evidence regarding the accuracy and effectiveness of PET/CT and other imaging modalities to evaluate treatment response in metastatic breast cancer is lacking, even though the types and results of imaging may strongly affect patient outcomes [24,25].

This literature review evaluates studies regarding the effectiveness of different imaging modalities in evaluating treatment response among metastatic breast cancer patients, and is part of a research project funded by the U.S. Agency for Healthcare Research and Quality (AHRQ). By reviewing the state of the science, we aim to inform future research efforts on this topic.

Materials and methods

Key questions

We developed key questions to guide our literature review in conjunction with the AHRQ and key informants in the field. Key questions focused specifically on the current use of imaging for the evaluation of treatment effects in metastatic breast cancer patients. These included: Which imaging modalities have been investigated for treatment response evaluation among metastatic breast cancer patients? What is the evidence for the comparative efficacy of these imaging modalities? What are the evidence gaps, or areas of uncertainty, requiring further research regarding imaging-based treatment evaluation of metastatic breast cancer patients?

Data sources and searches

With the assistance of a research librarian, we systematically searched PubMed®, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Cochrane Methodology Register, the Database of Abstracts of Reviews of Effects, the Health Technology Assessment Database, and the NHS Economic Evaluation Database for calendar years 2003 through 2013. We manually reviewed all reference lists of selected articles to identify additional studies. Finally, we searched imaging and oncologic websites to identify unpublished studies (i.e. gray literature), including the American Society for Clinical Oncology, American College of Radiology, American Cancer Society, National Comprehensive Cancer Network, Society for Nuclear Medicine, ClinicalTrials.gov, NIH Reporter, and ProQuest Dissertations and Theses. Specific search terms are described elsewhere (http://effectivehealthcare.ahrq.gov/).

Study selection

We included studies that matched our target patient population (patients with stage IV breast cancer), evaluated treatment response to chemotherapy outside of the breast, and provided estimates of outcomes measures. We developed inclusion and exclusion criteria (Table 1) and reviewed all titles and abstracts identified through our searches against them. We also retrieved and reviewed full-text articles for studies with an equivocal determination of inclusion based on a review of the title and abstract alone.

Given the rapidly evolving fields of medical imaging technologies and breast cancer systemic treatment regimens, we limited our review to all English-language publications from the last decade (2003–2013). We included all types of original investigations, and excluded letters, commentaries, editorials, and nonhuman studies. We focused our review on studies appraising imaging for treatment response evaluation, and therefore did not include studies where imaging was used for triaging patients for a future diagnostic test or studies that examined imaging used for surveillance purposes after treatment had ended.

Data extraction and synthesis

From the included studies, one investigator (LSG) abstracted details of the study setting, study design, type(s) of imaging, breast cancer patient inclusion criteria, breast cancer tumor characteristics, alternative methods of treatment evaluation (if any), length of follow-up data, and any patient outcomes associated with imaging findings. A second investigator (CIL) confirmed the extracted data elements. A consensus agreement between the two investigators was reached for any disagreement regarding study inclusion or data elements abstracted. The QUADAS-2 tool was used to evaluate the quality of studies [26]. Results of studies were not amenable to quantitative meta-analysis because of the various imaging modalities, outcomes, and measures. Therefore, we organized our review findings into succinct qualitative summaries.

Role of the funding source

The AHRQ funded this literature review under a contract to the University of Washington and Oregon Health & Science University Pacific Northwest Evidence-Based Practice Center. Researchers worked with AHRQ staff to define the scope and key questions, resolve issues arising from the literature review, and ensure that methodological standards were met. The AHRQ provided project oversight, reviewed draft technical reports, and distributed drafts for external review by outside experts. The final technical report is available at http://www.ahrq.gov/research/findings/evidence-based-reports/index.html. The AHRQ had no role in the selection, critical review, or synthesis of evidence. The study authors are solely responsible for the content of the manuscript.

Results

Our initial database searches identified a total of 159 potentially relevant published articles. After a detailed review by two investigators, 17 studies met our inclusion criteria (Fig. 1).

Characteristics of included studies are described in Table 2 and results in Table 3. In addition, we identified four relevant clinical