

Comparative Effectiveness of Magnetic Resonance Imaging in Breast Cancer

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The term *evidence-based medicine* was first coined by Sackett and colleagues¹ as “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.” The key to practicing evidence-based medicine is applying the best current knowledge to decisions in individual patients. Medical knowledge is continually and rapidly expanding, and it is impossible for an individual clinician to read all the medical literature. For clinicians to practice evidence-based medicine, they must have the skills to read and interpret the medical literature so that they can determine the validity, reliability, credibility, and utility of individual articles. These skills are known as critical appraisal skills. Generally, critical appraisal requires that the clinician have some knowledge of biostatistics, clinical epidemiology, decision analysis, and economics as well as clinical knowledge.

The Canadian Association of General Surgeons (CAGS) and the American College of Surgeons (ACS) jointly sponsor a program titled “Evidence-Based Reviews in Surgery” (EBRS), supported by an educational grant from Ethicon Inc and Ethicon Endo Surgery Inc. The primary objective of this initiative is to help practicing surgeons improve their critical appraisal skills. During the academic year, 8 clinical articles are chosen for review and discussion. They are selected not only for their clinical relevance to general surgeons, but also because they cover a spectrum of issues important to surgeons: for example, causation or risk factors for disease, natural

history or prognosis of disease, how to quantify disease (measurement issues), diagnostic tests and the diagnosis of disease, and the effectiveness of treatment. Both methodologic and clinical reviews of the article are performed by experts in the relevant areas and posted on the EBRS website. A listserv discussion is held in which participants can discuss the monthly article. Fellows and candidates of the College can access Evidence-Based Reviews in Surgery through the American College of Surgeons website (www.facs.org). All journal articles and reviews are available electronically through the website. Currently we have a library of 50 articles and reviews, which can be accessed at any time. Each October, a new set of articles will be available each month until May. Surgeons who participate in the current (modules) packages can receive CME credits by completing a series of multiple choice questions. Additional information about EBRS is on the ACS website or by email to the administrator, Marg McKenzie at mmckenzie@mtsinai.on.ca.

In addition to making the reviews available through the ACS and CAGS websites, 4 of the reviews are published in condensed versions in *the Canadian Journal of Surgery*, 4 in the *Journal of the American College of Surgeons*, and 4 in *Diseases of Colon and Rectum* each year.

REFERENCE

1. Evidence-Based Medicine Working Group. Evidence-based medicine. *JAMA* 1992;268:2420–2425.

SELECTED ARTICLE

Comparative Effectiveness of MRI in Breast Cancer (COMICE) trial: a randomized controlled trial

Turnbull L, Brown S, Harvey I, et al. *Lancet* 2010; 375:563–571

Question: Does the addition of MRI to standard triple assessment (x-ray mammography, ultrasound and fine needle aspiration cytology, or core biopsy)

compared to triple assessment alone reduce reoperation rates?

Design: Randomized controlled trial

Setting: Multicenter, which included 45 sites in the United Kingdom.

Patients: One thousand six hundred twenty-three women aged 18 years or older, with a history of biopsy-proven primary breast cancer.

Description of test and diagnostic standard:

Patients who were scheduled for wide local excision were randomly assigned to either MRI or no further imaging. X-ray mammography, ultrasound, and MRI were done according to standard protocol.

Main outcome: Proportion of patients undergoing a repeat operation or further mastectomy within 6 months of random assignment, or a pathologically avoidable mastectomy at initial operation.

Results: Addition of MRI to conventional triple assessment was not significantly associated with reduced reoperation rate, with 153 (19%) patients needing reoperation in the MRI group vs 156 (19%) in the no-MRI group, (odds ratio 0.96; 95% CI 0.75 to 1.24; $p = 0.77$).

Conclusion: The findings are of benefit to the National Health Service (NHS) because they show that MRI might be unnecessary in this population of patients to reduce repeat operation rates, and could possibly assist in improving NHS services.

Commentary: The local-regional treatment of breast cancer is guided by preoperative imaging studies in addition to physical examination. Determining the extent of disease and the presence or absence of multiple tumor foci, either within the same quadrant (multifocal) or in different quadrants of the breast (multicentric), determines whether a patient will be offered breast-conserving surgery or mastectomy. Multicentric disease in the breast has been reported to be associated with higher rates of ipsilateral-breast recurrence after conservative surgery, and therefore is generally considered a contraindication to breast-conserving approaches. Patients with multifocal disease are at higher risk of requiring additional surgical procedures in order to obtain histologically negative margins if the extent of disease is not recognized on preoperative imaging. The ideal preoperative imaging work-up would identify patients with multicentric disease who should proceed directly with mastectomy and those patients with multifocal disease with clear delineation of the extent of the disease, allowing the surgeon to excise the appropriate amount of tissue in order to achieve negative margins without the need for a re-excision.

The COMICE study assessed the benefit of adding preoperative breast MRI to this standard assessment. Breast MRI has the potential to identify multifocal disease and change the management in up to 20% of patients. By identifying disease and performing a more complete resection of disease, preoperative MRI could decrease the need for reoperation and also prevent local

recurrence of cancer. Although the study assessed the value of a diagnostic test, it actually did not compare MRI to a gold standard. Instead, it assessed the benefit of preoperative MRI in decreasing the need for further breast surgery or a mastectomy in the 6 months after randomization or a pathologically unnecessary mastectomy at initial operation. In other words, the investigators addressed a practical clinical question of whether the additional test changed clinical outcomes. This, of course, is more meaningful to many clinicians.

The trial was a randomized controlled trial that screened more than 5,000 patients and was conducted across 45 centers in the United Kingdom, suggesting that the data are generalizable. Eight hundred sixteen patients were randomized to MRI and 807 to no MRI. Patients screened for the study were already booked for wide local excision of their tumors, and half were randomized to an additional MRI. Patients found to have further abnormalities on MRI could undergo further MRI-guided biopsy.

Patients enrolled in the study were stratified according to the important variables of age, breast density, and consultant surgeon. Size of primary tumor, adequacy of margins, and extent of associated ductal carcinoma in situ (DCIS) were not used as stratification variables, emphasizing the pragmatic approach of the trial. Also the need for MRI-guided biopsy of suspicious areas was not required.

The results showed 19% of patients in each group underwent reoperation, with an odds ratio of 0.96 (95% CI 0.75 to 1.24, $p = 0.77$). Eight percent of patients in the MRI group had a mastectomy vs 2% in the no-MRI group. Sixteen patients in the MRI group (2%) underwent a pathologically avoidable mastectomy, as did 2 patients in the no-MRI group (<1%). Of the 16 patients undergoing avoidable mastectomy after MRI, only 3 actually had MRI-guided biopsy. The authors concluded that “the addition of MRI to conventional triple assessment had no benefit on reduction of reoperation rate.”

The strengths of the study include its adequate sample size, its well-defined MRI protocol, its intention-to-treat analysis, and its complete follow-up of patients. Also, the spectrum of patients and centers likely allows for generalization of the results.

The COMICE trial has several important limitations. It is unfortunate that the endpoints of this study were limited to the initial impact of MRI on surgical management and the study did not address the important question of recurrence rates with and without the guidance of preoperative MRI. To date, no randomized controlled trials have addressed this important outcome. Critics of MRI suggest that detecting subclinical disease

is unlikely to affect recurrence rates, similar to recent sentinel node trials that found no clinically relevant benefit in detecting additional disease on immunohistochemistry alone.

There are several subgroups of patients that might be expected to benefit more from preoperative MRI, but they were not specifically studied. The extent of disease tends to be underestimated in patients with invasive lobular carcinoma, very dense breasts, and those who are very young. Although the authors found no difference in outcomes in patients with lobular carcinoma compared with all other types, this subgroup was small (9% of the study group).

Finally, no information was provided on the interpretation of standard breast imaging in either group. There is increasing use of MRI to problem solve in specific situations where mammography with or without ultrasound is inconclusive. On the contrary, in cases of fatty breasts and where there is clear identification of the tumor with standard imaging, there is no benefit of adding MRI. Radiologic interpretation may be an important factor in determining those for whom MRI might be beneficial.

This study also highlights a number of critical points on the use of MRI. The rationale for MRI is to accurately identify extent of disease in an effort to reduce positive margin rates and identify patients who should undergo mastectomy for otherwise occult additional malignancy. It is imperative, however, that lesions detected on MRI are biopsied to confirm that they represent additional disease and are not false positives. This is illustrated in this study in the 16 patients who underwent an “avoidable mastectomy” up front. Only 3 had a biopsy of the area that MRI identified with disease, 6 patients did not have a biopsy, and the remaining had no data available. This highlights the absolute need to biopsy lesions identified on MRI before recommending a change in surgical treatment.

Overall, MRI has not been shown to be useful in decreasing the need for additional surgery in patients selected for wide local excision of breast cancer, and it is not required without specific indications outside a clinical trial.

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