

Conflicting Outcomes with Preoperative Breast MRI: Differences in Technology or Methodology?

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The controversies surrounding breast magnetic resonance imaging (MRI) have been both perplexing and frustrating, especially for surgeons and radiologists trying to decide whether or not to incorporate preoperative MRI as a standard of care. Mastectomy and re-excision rates have been alleged to go up, go down, or remain unchanged because of MRI. A randomized trial announced no benefit to preoperative MRI with regard to re-operation rates, but we cried foul¹ because its study design introduced MRI “mid-algorithm,” which is downstream, in our view, from its greatest potential benefit.

Most are in agreement that preoperative MRI will yield additional foci of cancer that can lead to mastectomy in some patients. However, this does not mean that the total number of mastectomies performed will increase proportionately, if at all, as many of these patients would have eventually undergone mastectomy anyway, without MRI. Still, a knee-jerk reaction by mainstream media and many physicians is that MRI is the primary cause of more mastectomies being observed nationwide. Additionally, critics have been concerned that the rate of “conversion to mastectomy” tends to exceed local recurrence rates.²

When investigators have looked beyond their “conversion to mastectomy” rates and have analyzed their entire cohort, the impact of MRI is not nearly so clear-cut, and it is becoming increasingly evident that MRI is not the sole cause of the rising mastectomy rate nationwide. In fact, careful studies are now showing that the mastectomy rate is rising independently of increasing MRI utilization. For instance, data from the Mayo Clinic in Rochester, MN, initially prompted concerns that MRI was the sole culprit behind rising mastectomy rates, but further analysis revealed that mastectomy rates increased from 2004 to 2006 predominantly among patients without MRI.³ Other studies show no impact at all of MRI on mastectomy rates.⁴ These total-cohort impact analyses are possible only through the study of all newly diagnosed breast cancer patients and, therefore, represent a different patient population than that seen in the COMparative effectiveness of MR Imaging in breast CancEr (COMICE) trial,⁵ which had a study design based on a cohort already selected for breast conservation therapy (70% of those assessed for COMICE eligibility were excluded), allowing only a unidirectional treatment vector, ie, conversion from lumpectomy to mastectomy.

In a recent article by Carpenter and colleagues,⁶ we see further support that preoperative MRI has a negligible overall impact on mastectomy rates. Carpenter and colleagues report their experience at Mayo Clinic in Phoenix/Scottsdale, AZ, with 814 newly diagnosed breast cancer patients (invasive disease only) of whom 232 underwent preoperative MRI. In this study, the use of preoperative MRI in invasive breast cancer patients increased over 5 years while the mastectomy rate remained unchanged. Seemingly inconsistent with this conclusion was the additional finding by Carpenter and colleagues of a change from breast conservation therapy to mastectomy in 19% of patients as a result of MRI findings.

At first glance, this 19% “conversion to mastectomy” rate should have resulted in more mastectomies overall, but it did not. Conservation rates held steady each year from 2003 through the first half of 2008, at an overall rate of 69%. Meanwhile, annual preoperative MRI utilization rates rose steadily from 19% to 45%. So, the question has to be posed: How can MRI steer patients from conservation to mastectomy in 19% of cases while the overall mastectomy rate remains unchanged? Carpenter and colleagues acknowledged that most of these “converted” patients were borderline candidates for breast conservation therapy, and it always must be considered that a significant percentage of “MRI-converted” patients would have opted for mastectomy anyway, without MRI, or that some would have eventually undergone mastectomy after multiple failed re-excision attempts.

Evidence is conflicting as to the impact of multiple re-excisions on recurrence rates, but even if one accepts that multiple re-excisions can accomplish low rates of recurrence, perhaps the largest study published (n = 2770) to support this position did so with 60% of patients undergoing re-excision, 8% of whom underwent 2 or more re-excisions (ie, 3 or more total surgical procedures).⁷ And, as with similar studies that include only selected patients who have undergone successful breast conservation therapy, we are not informed as to what percentage of the total cohort of newly diagnosed patients underwent failed conservation therapy or opted for mastectomy after positive lumpectomy margins. This is a key point because these patients who eventually undergo mastectomy may significantly overlap with the MRI “conversion to mastectomy” group.

If the only way in which MRI can “convert to mastectomy” without increasing the total number of mastectomies is through upfront identification of eventual mastectomy candidates, the variable that ought to change is the re-operation rate, where one should see a downward trend. Re-operation rates are a tenuous outcome measure, given the high variability among practices and protocols, but still, fewer re-operations should be seen in a total cohort with MRI utilization. However,

this effect is not necessarily demonstrated in non-randomized studies where MRI is used selectively, as seen in the above cited Carpenter and colleagues study where re-excision rates were unchanged.

Selective use of MRI imparts selection bias. Therefore, equivalent outcomes in either local recurrences or re-excisions between an MRI and non-MRI group could mask a benefit. For example, if MRI is used only in those patients with a predicted 15% local recurrence rate, and the actual outcome turns out to be a 5% local recurrence rate that is deemed “no different” than the non-MRI group, a benefit of MRI has been discredited. The reasons for selectively ordering MRI in the first place are also predictors of positive margins and local recurrences.

Young age, for instance, is perhaps the most consistent predictor of local recurrence after breast conservation therapy, and the oft-quoted Solin and colleagues article⁸ indicating a lack of MRI benefit is skewed toward younger patients undergoing MRI, by the authors’ admission. No analysis of breast density was included either. Additionally, there was a high re-excision rate (58%), ensuring the same low local recurrence rates noted above.⁷ It is noteworthy, too, that the study period was 1992–2001, during the developmental phase of breast MRI wherein it was often a unilateral procedure, except when a 2-day bilateral study was specifically requested. Thus, conclusions about contralateral outcomes await clarification.

To evaluate our claim that re-operations will be diminished in total cohorts of newly diagnosed patients, 2 approaches can be used: (1) studies of *consecutive* MRIs in newly diagnosed patients (as opposed to selective MRI use) or (2) preferably, a randomized trial where *all* newly diagnosed patients are included. While the COMICE trial’s strength is in its randomization, its weakness comes from a highly selected cohort that is not necessarily applicable to all women newly diagnosed with breast cancer. The purpose of COMICE through its selected cohort was to determine if MRI could help reach the UK National Health Service target of a 10% re-operation rate,⁵ not to study the overall impact of preoperative MRI in newly diagnosed breast cancer patients.

In our consecutive series⁹ that included data from an entire cohort, without selection bias, our re-operation rate of 8.8% in a large series of patients ($n = 603$) who underwent preoperative MRI would seem to support the outcome of fewer re-excisions with MRI use, especially when compared to the 60% re-excision rate noted above, in which the approach for defining clear margins appears to be the same as that used by us. However, because our single-institution study consisted of consecutively diagnosed patients, we did not have a concurrent control group, imparting a significant

limitation in attributing our low rate to MRI and in comparing our outcomes to those of other institutions.

Others, however, have reported improved outcomes with MRI in studies using concurrent controls. One study from the Netherlands¹⁰ reported incomplete tumor excisions in 19.4% of patients without MRI and in 13.8% with MRI ($P = 0.17$), and when evaluating only those women with invasive disease, the authors found a statistically significant difference ($P = 0.02$) between the 8.1% rate of incomplete excisions without MRI and a remarkably low rate of 1.6% with MRI. Some of these incomplete excisions were managed with an alteration in radiotherapy boost, but of those undergoing re-operations, the non-MRI group had more than twice the number of re-operations as the MRI group. We did not make the distinction between in situ versus invasive disease in our analysis,⁹ and our 8.8% re-operation rate after MRI was drawn from a disease mix of 75% invasive disease and 25% ductal carcinoma in situ (DCIS). The COMICE trial was skewed toward invasive disease (90%),⁵ yet it still had a 19% re-operation rate after MRI, which raises the question of what technological and/or methodological refinements are being used by those finding lower re-operation rates.

We began to formulate theories with regard to MRI impact when, in our aforementioned series,⁹ we found that our “conversion to mastectomy” rate was 7.7%, yet our total mastectomy rate *declined*, at least when compared to historical controls. The breast conservation therapy rate rose from 48% (the geographic norm) to 60% abruptly after initiation of our MRI program. Furthermore, contrary to expectations, when patients experienced a false-positive MRI, as defined simply by a callback for further study, our conservation rate was 70%. To explain the fewer mastectomies, we theorized a subtle effect of preoperative breast MRI not being addressed in most study designs, including COMICE, wherein MRI performed early in the diagnostic work-up resulted in the conversion of patients from mastectomy to lumpectomy. In this instance, there would be 2 vectors in our series: 7.7% toward mastectomy, but a larger vector in the other direction toward conservation.

At first, we considered differences in technology and/or interpretations as playing a major role in the different outcomes being reported. One feature of our work is that 100% of patients whose outcome data we analyzed were studied on a single, breast-dedicated MRI unit, the interpretations were made by breast radiologists with considerable experience with MRI (over 10 000 studies to date), and multiple quality improvement measures were in place. This approach eliminates numerous variables present in other studies wherein significant numbers of outside MRIs have been included. It is worth noting that in a recent survey of active members of the Society of Breast Imaging, a strong

majority of 561 respondents never (48%) or rarely (29.4%) interpreted breast MRI performed at an outside facility.¹¹

Although technological or interpretive differences may partly explain the differences in outcome data, we theorize that the differences may be due more to methodology than to technology, with preoperative MRI being utilized through 2 distinctive approaches: (1) routinely after a biopsy report confirms malignancy and (2) as requested by the surgeon after the patient is identified as being interested in breast conservation therapy *and* in the face of factors that make conservation success equivocal.

In the former instance (radiologist-directed and “non-pivotal” MRI), the patient has not yet been presented with therapeutic options, and at our facility, she will be counseled by the radiologist, a nurse navigator, and MRI techs, all reinforcing the notion that the MRI is being done to ensure that the patient is a good lumpectomy candidate and that the MRI may prompt a callback and possible biopsy. We agree with Carpenter and colleagues that this counseling process plays an important role in downplaying the impact of the MRI. At our institution, as soon as the preoperative work-up is complete, the actual MR and pathology images are presented at a pretreatment conference where the surgeon becomes familiar with the patient for the first time but *before* a discussion of options. A written report outlining conference conclusions for local-regional management is drafted by one of us (ABH) and forwarded to the primary care physician(s), who then has an opportunity to influence the patient’s care. Because our MRI unit is part of our mammography center, all of the above is accomplished prior to the patient’s first appointment with the surgeon.

We theorize that with the process described above, the patient perceives that MRI is performed to provide extra assurance of a safe lumpectomy, even if post-MRI biopsies were required (our conservation rate is 86% after negative biopsies). Also, the surgeon perceives the MRI results in the past tense, thus keeping MRI from serving in a pivotal role. Since the decision for conservation versus mastectomy is a complex interplay centering on both patient and surgeon, the completed MRI work-up might be influencing either or both.

In contrast, the approach used more often than ours is one in which the surgeon selects candidates for MRI, often ordered after a failed excision, where the emphasis turns MRI into a “pivotal” event. With this approach, MRI findings generate greater anxiety, and anxiety about lumpectomy leads to mastectomy. Furthermore, when MRI outcomes are published using this approach (as is true for all data so far with regard to local recurrence rates), there is a selection bias against the recognition of MRI benefit, as noted above. Many, but not all, of the patients in the Carpenter and

colleagues study appear to have been handled in this manner, perhaps explaining why re-excision rates were unchanged by MRI. Notably, the COMICE trial is designed only to test this latter “pivotal” approach wherein patients are randomized to MRI or no MRI *after* their candidacy for conservation therapy has already been established.

Space limitations prohibit extending this discussion to the controversies surrounding MRI findings in the contralateral breast, preoperative MRI for oncoplastic strategies, selection of patients for partial breast irradiation, the discovery of “elsewhere” invasive disease in patients diagnosed with DCIS, preoperative MRI as a baseline for post-treatment follow-up, and the use of MRI in neoadjuvant decisions. The cumulative benefit of these applications for preoperative MRI likely exceeds the isolated benefit to the ipsilateral breast, where MRI impact is muted by systemic therapy and whole-breast irradiation. Much of the criticism of preoperative MRI, though, has come through reductionism, wherein each potential benefit from the list above is isolated and attributed to have minimal impact, while the downsides are presented for the whole.

Additionally, critics have advised that surgeons should stick with the proven package of mammography, apparently forgetting that entry into the National Surgical Adjuvant Breast and Bowel Project B-06 randomized trial¹² of breast conservation was based on physical examination alone and, like the other landmark trials, preceded widespread use of mammography. In these trials, equal outcomes were accomplished, supporting a biological theory that was unrelated to whether or not someone had performed a preoperative mammogram.

Mammography is, of course, part of the inherent package of screen-detected cancers; however, for palpable cancer, mammography has never had its feet held to the fire of *P*-values as is currently being required of MRI. It seems odd that a tool with half the sensitivity of MRI is anointed as “proven,” without anything comparable to the COMICE trial in its historical development. In truth, surgeons adopted the use of preoperative mammograms for women with palpable tumors on the basis that a roadmap for surgery was desirable, a decision based on reason rather than empiricism. Preoperative MRI is simply an extension of this same rational process, only this time utilizing a technology with vastly improved sensitivity. Kuhl and colleagues cited guidelines from The Oxford Institute of Evidence-based Medicine, reminding us that randomized trials are not required for diagnostic tests that prove to be superior to established tests and that MRI has met this standard when used in the preoperative setting.¹³

Whether or not our theory of early, “non-pivotal” MRI in the preoperative work-up of newly diagnosed breast cancer

patients even lends itself to an empirical approach is uncertain. But if physicians were to awaken one day and find themselves restricted in action to only those endeavors that are *P*-value approved by empirical think tanks, we'd all be paralyzed before noon.

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