relevant in the early-line setting. However, the real value of this study lies in the prospective exploratory analysis of the usefulness of molecular imaging with [^{18}F]FDG-PET/CT as an "early readout" (here, at 1 week) to predict clinical outcomes in MBC for objective response rate, as measured by RECIST later in the treatment course. Essentially, this analysis compared very early [^{18}F]FDG-PET/CT to later assessment by conventional computed tomographic imaging, which remains the gold standard in MBC.

A predictive biomarker predicts whether a tumor will respond to a specific treatment intervention, usually a targeted therapy. For instance, the presence of HER2 amplification in breast cancer predicts a higher chance of response to trastuzumab therapy, with trastuzumab monotherapy producing an objective response in approximately one-third of patients.[3] Another way to predict response is to identify perturbed features of a system before and early after a treatment intervention that are robustly associated with response to therapy at a later time point. Molecular imaging ([^{18}F]FDG-PET/CT) is a good candidate for such a purpose, as it is readily available in the clinic, is reimbursable, and can be used to measure early metabolic changes in a tumor, for instance at 1 week after treatment initiation before changes in tumor size can be detected. Such early readouts could provide guidance for prompt switches in therapy, sparing patients the unwanted cost and toxicity of prolonged futile treatments and allowing a more efficacious therapy to be quickly implemented. In this study, the lack of a week-1 [^{18}F]FDG-PET/CT response was associated with failure to achieve an objective response by RECIST, with a negative predictive value of 91% for cohort 1 and 91% for cohort 2. Of note, the lack of a week-1 metabolic response in cohort 1 was associated with median progression-free survival of only 1.6 months, in contrast to 8.8 months in patients who showed an early metabolic response. These [^{18}F]FDG-PET/CT analyses are exploratory, and further confirmatory studies are needed before these findings can be adopted to guide routine clinical practice.

As our armamentarium of efficacious and toxic combinations for treating metastatic and HER2-positive breast cancers continues to grow, it is becoming more pressing to identify biomarkers that can predict response to specific therapies and to categorize patients who will do well with less toxic regimens. Combining molecular diagnostics and molecular imaging may be one avenue to help tailor therapies for cancer.

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DIAGNOSTIC IMAGING

The effects of population-based mammography screening starting between age 40 and 50 in the presence of adjuvant systemic therapy

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Adjuvant systemic therapy has been shown to be effective in reducing breast cancer mortality. The additional effect of mammography screening remains uncertain, in particular for women aged 40−49 years. We therefore assessed the effects of screening starting between age 40 and 50, as compared to the effects of adjuvant systemic therapy. The use of adjuvant endocrine therapy, chemotherapy and the combination of endocrine- and chemotherapy, as well as the uptake of mammography screening in the Netherlands was modeled using microsimulation. The effects of screening and treatment were modeled based on randomized controlled trials. The

effects of adjuvant therapy, biennial screening between age 50 and 74 in the presence of adjuvant therapy, and extending the screening programme by starting at age 40 were assessed by comparing breast cancer mortality in women aged 0−100 years in scenarios with and without these interventions. In 2008, adjuvant treatment was estimated to have reduced the breast cancer mortality rate in the simulated population by 13.9%, compared to a situation without treatment. Biennial screening between age 50 and 74 further reduced the mortality rate by 15.7%. Extending screening to age 48 would lower the mortality rate by 1.0% compared to screening from age 50; 10 additional screening rounds between age 40 and 49 would reduce this rate by 5.1%. Adjuvant systemic therapy and screening reduced breast cancer mortality in similar amounts. Expanding the lower age limit of screening would further reduce breast cancer mortality.

It is sometimes asked whether breast cancer screening is necessary in the era of adjuvant systemic therapies. In a recent article, de Gelder and colleagues used microsimulation modeling to assess (1) the effect of the introduction of adjuvant therapies on breast cancer mortality, (2) the additional effect of mammographic screening, and (3) the joint effect of both. The authors calibrated the model to fit breast cancer incidence and mortality data in the Netherlands. Two crucial findings were that screening at ages 50 to 74 years conferred a substantial reduction in breast cancer mortality in addition to that of adjuvant systemic therapies and that lowering the screening age to 40 years, with annual screening at ages 40 to 49 years, would further reduce mortality from the disease. The additional reduction in mortality as a result of screening at ages 50 to 74 years was of similar magnitude to that of the systemic therapies (around a 15% reduction), from 58 to 49 deaths per 100 000 woman years. Reducing the minimum age to 40 years resulted in a further projected relative reduction of 5%, or 46 deaths per 100 000 woman years.

The results make sense. While there is no doubt that adjuvant systemic therapies have conferred better survival in patients with breast cancer, including at advanced stages, it remains the case that even in the 21st century, there is a substantial survival advantage from diagnosis at an earlier stage.[1] Similarly, the further reduction in mortality, albeit smaller in absolute terms, as a result of lowering the screening age to 40 years is consistent with both randomized trial and service screening results.[2,3]

Furthermore, the results are consistent with observed incidence and mortality rates, with 1 exception: an additional unattributed decrease in mortality of about 1% per year had to be included in the model to obtain a good fit to the Netherlands data. This too is not unexpected. Both the adjuvant systemic therapies and the screening have changed since the early 1990s, when their use began to flourish. In the interim, the adjuvant therapies have evolved to include aromataze inhibitors, taxanes, and other therapies, and film mammography has been replaced by digital mammography. One would expect the reduction in breast cancer deaths to accelerate in response to these developments.

The effects of screening may seem modest partly because these effects pertain to breast cancer mortality at ages 40 to 84 years. Screening at ages 50 to 74 years would confer no survival benefit at ages 40 to 49 years, and screening at ages 40 to 49 years is assumed to have no effect on mortality at ages 75 to 84 years. It is also worth noting that the effect of screening, in addition to the effect of adjuvant systemic therapies, at ages 50 to 74 years was estimated to be almost exactly equal to that of the adjuvant therapies themselves.

In relation to this study, it would be interesting to see the results the other way around: what is the effect of screening in the absence of adjuvant systemic therapies, and what is the marginal benefit of those therapies in addition to the mortality reduction conferred by screening? This would be of interest since diagnosis essentially precedes therapy.

One would anticipate that in such an analysis, adjuvant systemic therapies would add a further mortality reduction in addition to the effect of screening. Both screening and adjuvant systemic therapies have been shown in randomized controlled trials to prevent deaths from breast cancer, and whatever our own opinions about relative benefits, we should accept that both have contributed to a revolution in breast cancer survival in recent decades. It is gratifying that high-quality microsimulation modeling results also indicate this. When I started work in breast cancer control in 1979, the great majority of breast cancer patients died of the disease. Now, the opposite is the case. This should be a source of satisfaction to all involved with breast cancer prevention, diagnosis, and treatment.

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Adding MRI to ultrasound and ultrasound-guided fine-needle aspiration reduces the false-negative rate of axillary lymph node metastasis diagnosis in breast cancer patients

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Aim.—To evaluate whether adding magnetic resonance imaging (MRI) to ultrasound (US) and US-guided fine-needle aspiration (US-FNA) can reduce the false-negative rate (FNR) in the diagnosis of axillary lymph node metastasis (ALNM) in breast cancer patients, and to assess false-negative diagnosis of N2 and N3 disease when adding MRI to US and US-FNA.

Materials and Methods.—From March 2012 to February 2013, 497 breast cancer patients were included in the study. ALNM was evaluated according to US and US-FNA prior to MRI. Second-look US was performed when MRI showed positive findings of ALNM. If second-look US also revealed a positive finding, US-FNA was performed. Diagnostic performance, including FNR, was calculated for US and US-FNA with and without MRI. The negative predictive value (NPV) of N2 and N3 disease was evaluated in negative cases based on US and US-FNA with MRI.

Results.—A total of 159 of 497 (32.0%) patients were found to have ALNM. Among them, 92 patients were diagnosed with metastasis on US and US-FNA. When adding MRI to US and US-FNA, an additional six patients were diagnosed with metastasis. The FNR of diagnosis of ALNM was improved by the addition of MRI (42.1% versus 38.4%, $p = 0.0143$). The NPV for N2 and N3 disease was 98% (391/399) based on US and US-FNA with MRI.

Conclusion.—Adding MRI to US and US-FNA could reduce the FNR of the diagnosis of ALNM. Furthermore, US and US-FNA with MRI may exclude 98% of N2 and N3 disease.

This study by Hyun and colleagues from the Republic of Korea has value in determining whether the false-negative rate of axillary lymph node metastasis (ALNM) in breast cancer patients can be reduced by adding MRI to ultrasound (US) and US-guided fine-needle aspiration (US-FNA). As reported in this article, the false-negative rate was reduced from 42.1% to 38.4% with the addition of MRI. The addition of MRI led to the identification of six additional cases with ALNM. This article contributes to the growing body of breast imaging literature supporting the preoperative diagnosis of axillary metastatic disease prior to sentinel lymph node biopsy or axillary dissection.

One limitation noted by the authors was interobserver variability with US. Interpretation of US may vary greatly among radiologists, especially when comparing imagers with different levels of experience. Furthermore, there is a range of skill levels in performing US-FNAs.

When morphologic criteria are used in addition to the measured cortical thickness, the sensitivity and specificity of US-FNAs are improved.[1] Mainiero and colleagues[2] showed a sensitivity of 94% and a specificity of 72% when focal cortical thickening was incorporated into US evaluation.

In this study, inadequate FNA samples were considered negative results. This method of classifying inadequate samples is a weakness, as inadequate or non-diagnostic samples require repeat FNA. At our institution—The University of Texas MD Anderson Cancer Center—FNAs are immediately assessed by a cytologist to determine the adequacy of sampling and to render a preliminary diagnosis.

This article highlighted an approach to improving the preoperative diagnosis of ALNM. Adding MRI to US and US-FNA may result in a decrease in the number of unnecessary sentinel lymph node biopsies and assist in neoadjuvant chemotherapy planning.

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