Digital Breast Tomosynthesis May Improve Breast Cancer Detection Rates

A recent prospective study has indicated that integrated 2-dimensional (2D) mammography and digital breast tomosynthesis (DBT) with 3-dimensional (3D) images may improve breast cancer detection and reduce false-positive readings (Lancet Oncol. 2013;14:583–589).

Standard 2D mammography is limited by the superimposition of breast tissue, which can interfere with reading by concealing cancers or making normal tissue appear abnormal. DBT technology uses several radiographs to reconstruct a pseudo-3D image. Investigators set out to determine whether this technology had advantages over standard mammography.

“I like to compare standard mammography–film/screen as well as digital–to a book with clear pages,” explains Daniel Kopans, MD, who is the senior radiologist in the breast imaging division at the Massachusetts General Hospital in Boston and the inventor of DBT, but was not involved in this study. “You can hold the book up to the light and see all the words, but they are superimposed on one another so that they are hard to read. DBT allows you to look at each page individually.”

The Screening with Tomosynthesis OR standard Mammography (STORM) trial, which was conducted from August 2011 through June 2012, was a prospective, population-based breast cancer screening study that compared mammography screen reading in 2 phases: standard digital 2D-only versus integrated digital 2D and digital breast tomosynthesis with 3D images. The patients had mammograms on a unit that takes 2D and 3D images at the same examination with one breast position and compression per view. Each 2D and 3D screening examination consisted of a bilateral 2-view mammogram. Therefore, each woman had paired results for each screening examination. The participants were asymptomatic women undergoing routine screening.

Screening tests were interpreted in 2 ways: a radiologist first looked at the 2D image and issued a report, and the same radiologist on the same day then issued another report based on integration of the 2D and 3D images. Radiologists had to decide whether to recommend recall of a patient after reading the 2D image alone, and then again after the integrated reading. Primary outcomes were the numbers of cancers detected and the numbers and percentage of false-positive recalls, as well as the incremental cancer detection rate attributable to integrated 2D and 3D screening.

Increased Detection Rates

Population-based breast cancer screening programs in Trento and Verona, Italy examined 7292 women (median age, 58 years) and detected 59 cancers (52 invasive and 7 ductal carcinoma in situ) in 57 participants. Thirty-nine cancers were detected on both the 2D reading and the integrated 2D and 3D reading. Another 20 cancers were found only by the integrated 2D and 3D reading. No cancers were detected by the 2D reading that were not also recognized on the integrated 2D and 3D reading.

Furthermore, significantly more cancers were detected with the integrated reading; 5.3 cancers per 1000 screens were found with 2D reading alone versus 8.1 cancers per 1000 screens for integrated 2D and 3D readings (P < .0001). This represented a 33.9% increase in the cancer detection rate. The increased detection rate was similar between women with low-density breast tissue and those with...
high-density breast tissue, but the small number of women with high-density breast tissue limited the density-stratified analysis.

A total of 395 screenings resulted in false-positive readings (5.5%). Of these, 181 occurred from both readings. However, 141 false-positive results were found with 2D screens, and 73 were found with integrated 2D and 3D screens \((P < .0001)\).

“Overall, we need to keep in mind that although the data on DBT are very exciting, we have relatively little evidence from large screening trials, so one has to proceed with some caution,” says Nehmat Houssami, MPH, PhD, corresponding author and associate professor at the Sydney School of Public Health at the University of Sydney Medical School in Sydney, New South Wales, Australia.

Dr. Houssami and her colleagues noted that they studied comparative cancer detection between 2D-only and integrated 2D and 3D screens, not absolute screening sensitivity. They found significantly more breast cancers using the integrated technique as well as fewer false-positive readings. Based on these data, the authors noted that false-positive recalls could be reduced by approximately 20% using integrated 2D and 3D screening.

“Usually in order to detect more cancers (increased sensitivity) you have to lower your threshold of suspicion and that leads to more recalls (decreased specificity). DBT is unusual since it improves both sensitivity and specificity,” Dr. Kopans observed.

The STORM investigators also noted that no other screening trials to date have reported final results using DBT. There is a preliminary report of a trial performed in Oslo, Norway, that did demonstrate significantly increased detection rates using integrated 2D and 3D mammography as well as reduced false-positive findings in over 12,000 women screened during the first year of the trial \((\text{Radiology}. \ 2013;267:47-56)\). The increased detection rate of 30% reported in the Oslo trial was similar to that in the STORM trial.

Furthermore, in the STORM trial, the 3D images were not interpreted independently of the 2D images, and therefore conclusions regarding DBT with 3D images alone cannot be made. “We have no evidence that the 3D mammogram can substitute for the 2D mammogram, and radiologists rely on the 2D images to form an opinion,” says Dr. Houssami. “Small studies, clinical series-type studies, have looked at this issue and have not come up with consistent findings.”

Limitations of the STORM study include the fact that repeat screenings were not evaluated and therefore the increased cancer detection rate may not continue (or may be lower) with repeated screenings. Likewise, the study did not measure whether increased detection decreased the breast cancer mortality rate, nor did it examine whether interval cancer rates decreased at subsequent screenings.

Another consideration is radiation dose. The average dose from 3D imaging is approximately the same as 2D imaging, and therefore integrated 2D and 3D imaging roughly double radiation exposure. However, there is technology recently available that allows 2D images to be reconstructed from the 3D images, thus eliminating the need for separate 2D images to be taken.

Should DBT Be a Standard Test?

Given the STORM trial findings, Dr. Houssami recommends that more studies are needed before DBT with 3D imaging is made a standard test for breast cancer screening.

“Recommendations for population screening should be based on solid, consistent evidence coming from several large screening trials,” Dr. Houssami says. “On this basis, we recommended awaiting replication of our findings from other studies as the next step. So far, we have results from only 2 large screening studies: our study based on double-reading as practiced in European screening programs, and interim results from the Oslo study. Additional screening trials using DBT are in progress, and are expected to provide relevant results in the near future,” says Dr. Houssami.

However, DBT is being offered in the community. Dr. Houssami says she would support the decision to have the integrated 2D/3D screening over standard mammography if a woman is fully informed of the available data.

By contrast, Dr. Kopans does not think it is premature to recommend digital breast tomography for general breast cancer screening. “Mammography has been shown in randomized, controlled trials to reduce the death rate from breast cancer,” Dr. Kopans adds. “DBT is a better mammogram. It simply makes sense to find more cancers early while decreasing the recall rate.”

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Predictive Biomarkers May Help Individualize Treatment for Patients With Follicular Lymphoma

Researchers have identified a subgroup of patients with follicular lymphoma who derive greater benefit from bortezomib with rituximab versus rituximab alone (Clin Cancer Res. 2013;19:2551-2561).

Patients with follicular lymphoma, which is a heterogeneous disease, vary with regard to their disease course and responsiveness to treatment. As with other malignancies, there is an effort to individualize therapy by finding disease characteristics that predict responsiveness to a particular treatment. Predictive biomarkers would be especially helpful in patients with follicular lymphoma because there are multiple treatment options. Researchers set out to determine whether they could find such a tool to help individualize the treatment of patients with follicular lymphoma.

Bertrand Coiffier, MD, PhD, professor of hematology and head of hematology in the department of hematology at the Hospices Civils de Lyon and Claude Bernard University, both in Lyon, France, and his colleagues reported on a subset analysis of the previously reported phase 3 LYM-3001 study. The LYM-3001 study randomized nearly 700 patients with relapsed or refractory follicular lymphoma to receive bortezomib plus rituximab or rituximab monotherapy (Lancet Oncol. 2011;12:773-784). It demonstrated statistically significant improvements in the response rate (63% vs 49%) and progression-free survival (PFS) (12.8 months vs 11 months) for patients treated with bortezomib and rituximab versus those treated with rituximab alone, but no overall survival advantage was noted.

This subset analysis reports on an exploratory endpoint biomarker analysis that was preplanned in the study protocol. Potential biomarkers were prespecified and included proteins as well as genes that were chosen because of their attenuation by bortezomib, association with poor prognosis, or relation to rituximab activity.

Biomarker Pair Correlates to Response

Researchers first evaluated associations with single markers and found several markers that correlated significantly with PFS benefits, but the advantage was mostly fewer than 5 months or the frequencies were low. Next, analysis was performed pairing biomarkers and 1140 comparisons were made. In all, 14 biomarker pairs demonstrated a greater than 6-month increase in PFS for patients treated with bortezomib and rituximab versus those receiving rituximab alone.

One pair of biomarkers, the gene PSMB1 P11A C/G heterozygote and 50 or fewer CD68-positive cells, remained significantly associated with increased PFS with combination therapy after a statistical correction called the “false discovery rate” was applied. The cell number of CD68 was determined by taking the average of 3 separate high-power fields. This biomarker pair was subsequently tested under different genetic models. Researchers found that with low CD68, the PSMB1 P11A gene with the G allele (C/G3G/G) was significantly associated with PFS.

A total of 376 patients (186 of whom were treated with bortezomib and rituximab and 190 of whom were treated with rituximab alone) were evaluated for both the PSMB1 P11A gene and CD68 positivity. A total of 164 patients (44%) were biomarker positive, namely, they had the biomarker pair that was identified as being associated with better outcomes with the addition of bortezomib (PSMB1 P11A with the G allele and low CD68 expression). Of these, 78 patients were treated with bortezomib and rituximab and 86 were treated with rituximab alone. In biomarker-positive patients, PFS was found to be significantly longer in patients treated with bortezomib and rituximab versus those treated with rituximab alone (14.2 months vs 9.1 months; P < .0001).

The response rate was also significantly higher in the combination group. Overall survival appeared to be longer, with a hazard ratio of 0.49, but after statistical correction, it was not found to be statistically significant. No difference with regard to the safety of the regimen was noted between groups. In biomarker-negative patients, no difference in outcomes was noted between the treatment groups.
Results in Context

Dr. Coiffier says he considers the study results robust enough to recommend the biomarker pair as a basis for treatment choice, but it is not clear that the regimen of bortezomib and rituximab should be the treatment of choice among patients with follicular lymphoma.

“The question of whether this combination would be used in the treatment of follicular lymphoma will depend on the efficacy/toxicity of other possible treatments,” says Dr. Coiffier. “There are currently a lot of new, mostly targeted drugs available for this lymphoma and the future choices will depend on the results of not-yet.completed phase 3 studies.”

Bruce Cheson, MD, deputy chief of hematology-oncology and head of hematology at Georgetown Lombardi Comprehensive Cancer Center in Washington, DC, says it is critical to include correlative studies whenever possible in clinical trials, but knowing which studies to include is not always clear.

“It is critical to include correlative studies whenever possible in clinical trials, but knowing which studies to include is not always clear. Only through incorporating predictive biomarker evaluation in clinical trials will we eventually reach the goal of personalized treatments,” Dr. Cheson says. While he finds the current study intriguing, he believes its applicability is limited because the LYM-3001 trial did not meet the prespecified improvement in PFS that was written in the protocol, even though the addition of bortezomib significantly increased the PFS.

“We have more exciting novel agents in clinical trials for relapsed follicular lymphoma such as ibrutinib, idelalisib, IPI-145, and ABT-199,” Dr. Cheson adds. “For studies of these agents, correlative biomarker analysis will be critical for further development.”

The authors conclude that this prespecified subset analysis suggests that a predictive biomarker for increased PFS in response to the combination of bortezomib and rituximab exists in patients with follicular lymphoma. The study was one of the largest to date performed in patients with relapsed and refractory follicular lymphoma, adding to the strength of the findings. In addition, the biomarker analysis was planned, not a retrospective review of data. Furthermore, a high percentage of the population (43.6%) was biomarker-positive and combination therapy was found to significantly improve outcomes, thus indicating clinical usefulness.

However, the authors point out that it was an exploratory analysis, despite being prespecified in the protocol, making independent validation studies a requirement. Importantly, testing for the markers would be feasible; CD68 can be detected by immunohistochemistry and the authors state that the genotyping assay used to identify PSMB1 P11A was straightforward and that developing a validated assay for commercial use could be done.

The current study is a step in the direction of individualized therapy to improve outcomes in patients with lymphoma, but future work with other therapies is crucial. “There clearly will be other biomarkers in follicular lymphoma that will emerge as predictive for therapy response, such as current work looking at activity of the pathways related to the B-cell receptor,” Dr. Cheson says.

Dr. Coiffier agrees and adds that while multiple prognostic markers are well characterized, predictive markers for newer targeted agents are lacking and analysis of responding patients in phase 3 studies must be performed.

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