New Techniques in Interventional Radiology in Oncology

Radiological imaging has a number of important applications in oncology, including detecting the primary tumor and determining the extent of disease for staging. Radiation is used for planning cancer treatment, administering image-guided therapy, assessing response to therapy, and monitoring disease activity.

Digital Tomosynthesis of the Breast

While mammography provides a 2-dimensional image of a 3-dimensional space, digital breast tomography (DBT) allows visualization through dense overlapping tissue to better characterize breast structures for diagnostic purposes. According to Mark Helvie, MD, University of Michigan, Ann Arbor, Michigan, USA, DBT has potential for better screening sensitivity and a lower recall rate compared with digital mammography (DM). DBT employs limited-angle cone-beam computed tomography (CBCT) that takes multiple low-dose exposures at angles from 10° to 60°. The radiation dose can range from equal to or twice that of conventional imaging. Reconstruction algorithms create image slices from different depths of the breast; the slices are read at 1-mm to 10-mm thicknesses.

Early data, although not robust, show that DBT is generally preferred by readers. More masses are detected with better mass characterization. Studies that have compared DBT with diagnostic DM show that 45% more mass margin detail can be seen with DBT. A study of 67 masses that used 4 blinded readers found that DBT performed at least as well as DM spot views [Noroozian M et al. *Radiology* 2011].

Bernardi et al. [*Breast Cancer Res Treat* 2012] demonstrated a 74% reduction in recalled cases, all for noncalcification, with no false negatives, in 158 DM screen recalls. Wallis et al. [*Radiology* 2012] reported recall reductions of 11% for 2-view DBT and 10% for single-view DBT.

DBT challenges include calcification detection, dose and protocol choices, physician training, lack of real-life experience with recall rates, and longer reading time (>2 times DM). Spangler et al. [*Am J Roentgenol* 2011] found calcification detection rates of 90% with DM versus 80% with DBT in malignant tumors and 81% with DM versus 68% with DBT in benign tumors. Although the difference was not statistically significant (ROC 0.76 vs 0.72), it appears that calcification detection is better with DM.

Screening is potentially the most important use for DBT, but there have been no randomized trials that have demonstrated improved mortality. Currently, the US Food and Drug Administration (FDA) considers 2-view DBT (Hologic) to be supplemental to 2-view DM.

Incremental improvement in sensitivity occurs with incremental images and doses. Taking a craniocaudal view in addition to a mediolateral oblique view improves sensitivity and specificity by 5% to 15%. Diagnostic recalls improve specificity by up to 90%. Gennaro et al. [*Eur Radiol* 2010] found that ROC was similar with single-view DBT (0.851) and 2-view DM (0.836). A study of 2-view DM alone versus single-view DBT alone found little difference in sensitivity, but combining single-view DBT with orthogonal DM resulted in a 12% increase (p=0.026). An 11% advantage for detecting masses and calcifications was observed with 2-view DBT (ROC 0.85) versus 2-view DM (ROC 0.77; p=0.02) [Wallis et al. *Radiology* 2012], but this improvement occurred only with less experienced (<10 years) readers.

In the Hologic system FDA submission studies, there was a significant 7% improvement in ROC AUC with DBT plus DM versus DM alone (Table 1). Noncancer recall was decreased by 38% in Study 1 and by 19% in Study 2. Sensitivity decreased by 8% in Study 1 and was neutral in Study 2, which was felt to be a teaching and threshold issue. A University of Pittsburgh study showed that with increased training, the detection rate was increased by 5%. In these studies, virtually all improvement occurred with masses versus calcifications.

Table 1. 2 View DBT Plus 2 View DM.

Study	ROC AUC	Cancer Recall	Non-cancer Recall
Reader Study 1	7% (4%, 11%)	-8% (-15%, 0%)	-38% (-30%, -46%)
Reader Study 2 (University of Pittsburg Study*)	7% (4%, 10%)	0%	-19%
	7%, 12%	5%	-12%

*The Pittsburgh Study used two methods to calculate the change in ROC AUC; both methods were different than the method used by Hologic. The Pittsburgh Study used 2-view FFDM plus 2-view DBT (MLO and CC); Reproduced with permission from M. Helvie, MD.

Early experimental DBT studies show promise for improved mass detection and characterization. Imaging sequences and dose choices will vary, depending on the objectives and technological advances. Detection of calcifications requires further study. Clinical application requires reader training and longer reading times. Given the current controversial screening environment, larger-scale clinical trials are needed to demonstrate screening effectiveness.

Interventional Oncology of the Liver

According to Jean-Francois Geschwind, MD, Johns Hopkins University, Baltimore, Maryland, USA, interventional oncology is a hybrid between surgery and radiology, with an emphasis on therapeutic procedures. Precise image guidance is used to access tumors by intraarterial and intratumoral approaches. Drug delivery is improved using techniques, such as drug-eluting microspheres, remote activation, and isolated perfusion.

Most patients with hepatocellular carcinoma (HCC) have intermediate-stage disease at diagnosis. Established therapies for this population are transcatheter arterial chemoembolization (TACE), TACE with drug-eluting beads (DEB-TACE), and radioembolization using yttrium-90 radioactive microspheres. The combination of DEB-TACE plus sorafenib is being evaluated in clinical trials.

TACE significantly improved overall survival (26% to 29%) in studies by Llovet et al. [*Lancet* 2002] (p<0.009) and Lo et al. [*Hepatology* 2002] (p=0.002), with sustained objective response rates (3 to 6 months) of 35% to 39%. These studies led to the adoption of chemoembolization as the treatment of choice for intermediate and advanced HCC. TACE is also established as standard therapy in patients who await liver transplantation.

Improved tumor targeting is achieved with dual-phase CBCT, and response is assessed with 2-dimensional perfusion software. Varela et al. [*J Hepatol* 2007] reported a 75% response rate with DEB-TACE using doxorubicin in 27 patients with Child-Pugh A disease. One- and 2-year survival rates were 92.5% and 88.9%, respectively, at a median follow-up of 28 months. The Prospective Randomized Study of Doxorubicin in the Treatment of Hepatocellular Carcinoma by Drug-Eluting Bead Embolization [PRECISIONV; NCT00261378] trial demonstrated significantly lower rates of doxorubicin-related adverse events with DEB-TACE versus conventional TACE (p=0.012) [Lammer J et al. *Cardiovasc Intervent Radiol* 2010]. In a Johns Hopkins Phase 2 study, median survival with DEB-TACE was 26 months in patients with unresectable HCC.

Radioembolization using yttrium-90 microspheres delivers higher-radiation doses to smaller volumes, providing greater tumoricidal effect and minimizing damage to normal tissue. Several studies have demonstrated the utility of radioembolization in patients with a large tumor burden, multifocal disease, or portal vein thrombosis (PVT). A German study on radioembolization reported a median survival of 16.4 and 10.4 months in patients with and without PVT, respectively.

The combination of DEB-TACE plus sorafenib exploits the proangiogenic effects of TACE. The Phase 3 Study of Sorafenib in Patients With Advanced Hepatocellular Carcinoma [SHARP; NCT00105443] demonstrated an overall survival benefit with sorafenib (10.7 months) versus placebo in patients with HCC (7.9 months; HR, 0.69; 95% CI; 0.55 to 0.87; p<0.001) [Llovet JM et al. *N Engl J Med* 2008]. These results led to the Johns Hopkins Phase 2 trial of doxorubicin-eluting LC bead TACE plus sorafenib in patients with unresectable HCC [NCT00844883]. Grade 3/4 toxicity results were not worse with the combination versus sorafenib or DEB-TACE alone. Early results showed a 96% tumor response rate (RECIST) with DEB-TACE plus sorafenib (Table 2). An ongoing ECOG Phase 3 study is recruiting for a randomized, double-blind comparison of TACE with and without sorafenib in patients with unresectable HCC.

Table 2. Tumor Response: Phase 2 Trial of DEB-TACE Plus Sorafenib.

Features	Pre-DEB-TACE	Post-DEB-TACE	Change at 3 weeks (%)	p value
Tumor Size±SD (cm)	7.9±4.3	7.6±4.5	-4	0.79
Tumor Enhancement (%)	85	43.5	-49	<0.01
ADC* (x10^{-3} mm 2/s)	1.2	1.54	25%	0.01
EASL Partial response: 14/26 (54%) Stable disease: 12/26 (46%)		RECIST Stable disease: 25/26 (96%) Progressive disease: 1/26 (4%)		

*ADC measured by functional diffusion weighted MR; Reproduced with permission from JF Geschwind, MD.

TACE is the gold standard. DEB-TACE using doxorubicin has improved efficacy and fewer side effects compared with TACE. DEB-TACE has a growing role, pending outcomes of clinical trials. There is a strong rationale for combining intraarterial therapies with sorafenib, which has demonstrated excellent safety in preliminary results.

Changing Cancer Paradigm After the United Nations Summit

Putting Cancer on the Global Agenda

John Seffrin, PhD, American Cancer Society, Atlanta, Georgia, USA, discussed the historical significance of the United Nations (UN) High-Level Meeting, the outcomes of the May 2013 65th World Health Assembly, the role of nongovernmental organizations (NGOs), and critical objectives to take advantage of the new global cancer paradigm. "We are seeing the beginning of a tsunami of avoidable, often preventable noncommunicable diseases," Dr. Seffrin said. "Cancer could become the number one leading cause of death in the not-too-distant future."

Dr. Seffrin shared that the outcomes document from the UN High-level Meeting essentially says four things: 1) Cancer and