Clinical applications

3D ultrasound in neoadjuvant therapy of breast tumors

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In neoadjuvant therapy of breast lesions a needle biopsy is performed in place of conventional excisional biopsy, after which the mass is left in situ in order to determine the effect of the therapy. The rationale for this approach is that removal of the tumor and lymph nodes would also eliminate a valuable gauge for measuring the success of therapy. Leaving the mass within the breast provides a metric to visually determine whether or not the first line treatment is working.

Ultrasound offers an ideal platform for monitoring the effect of therapy. Its advantages include the absence of ionizing radiation, the widespread availability, and the relative ease of use. However, neoadjuvant therapy requires high-quality imaging and accurate measurement for regular and ongoing measurement of tumor volume.

At the University of Kansas Breast Cancer Prevention Center, the effects of neoadjuvant therapy are monitored using the Philips iU22 ultrasound system. The iU22 ultrasound system with Vision 2009 is an “intelligent” system, offering fast acquisition of a complete volumetric data set, with immediate availability of volume imaging, and automated quantification.

Automated quantification

Automatic quantification can detect and measure very subtle changes in the tumor volume. Shrinkage within 48 hours can indicate successful therapy, while continued growth may indicate the need for a new approach, such as changing the drugs or going straight to surgery. Accurate measurement is therefore critical.

We have found automatic quantification to be far more accurate than a physical breast examination performed by a nurse or clinician, and is much less expensive than an MRI scan. The accuracy of the measurement is particularly important because it is essentially a two-dimensional measurement of a three-dimensional volume, so that a very small change in the diameter of the mass indicates a significant change in the volume.

An increase in the size of the tumor is not necessarily an indication of a failed therapeutic effort. A successfully treated tumor may rapidly swell as a response to injury, like a bruise, showing the rapid death of a primary index cancer.

Another, novel indicator is quantification of the vascularization. Changes in the vascularity of a tumor can be observed quickly, painlessly, easily, consistently and often. This information could become an accurate predictor of the success or failure of therapy.

The VL13-5 transducer

The iU22 is provided with the new VL13-5 3D linear array transducer (Figure 1). This transducer combines an easy-to-use ergonomic design with state-of-the-art imaging capabilities, including Tissue Aberration Correction (TAC). TAC is a new technology that corrects for the different speeds of sound associated with different tissue types, such as fat and glandular tissue in the breast, resulting in sharper images with better spatial resolution and less clutter.

3D imaging

The VL13-5 transducer acquires a complete volumetric data set in a single run, while 3D imaging derived from the data set can show the full extent of a tumor, with accurate definition of the tumor margins, including microlobulations, septa, and spiculations (Figures 2, 3). This contributes to precise measurement of the tumor volume.

Figure 1. The VL13-5 transducer. The convex face allows 3D volumetric automated imaging in two perpendicular planes.
Another simple but important benefit of 3D imaging is its ability to show the exact position of the biopsy needle. Conventional imaging can give the impression that the needle is within the tumor when, in fact, it lies alongside it.

**New insights**

3D imaging also provides valuable additional information on tumoral growth patterns and the way cancers spread. We have recently observed that breast cancer tends to spread in the coronal plane, so we have selected our volumetric acquisition in such a way as to maximize diagnostics and evaluation in this plane. In our view, measurements in the coronal plane provide the most accurate measure of breast cancer growth and the most accurate measurement of the response to treatment.

**Off-site evaluation**

The ability to acquire and store a complete volumetric data set for later evaluation has proved to be a major benefit. The need to maintain patient throughput puts a certain amount of pressure on the radiologists, making it difficult for them to assess masses in the examination room. The iU22 image clips are saved to PACS, allowing the images to be reviewed off-site in a peaceful viewing room, so that the oncologist can study the image data at a high level of detail, without interruptions.

**Improved workflow**

The iU22 with Vision 2009 has had significant benefits for the workflow. Departments doing breast imaging are constantly under pressure to do faster imaging more consistently. It is critical for the sonographer to spend as much as time as possible looking for cancer rather than typing data during the initial study. The Philips iU22 incorporates a one-button prompt protocol to lead the sonographer through the breast and locate the probe.

Smart protocols overcome the problems of labeling, where the reader had to type in the location in the breast, the distance from the nipple, the radial or antral radial orientation, and so on. This can easily require up to 200 key strokes for a single breast, with the risk of skipping key areas. With the smart protocols, the reader is prompted by a screen-driven message: left breast, 2 o’clock, anti-radial, etc. This avoids time wasted in labeling, and helps to ensure accurate, motivated imaging.

Figure 2. Slice from the 3D data set showing a 7.9 mm malignancy. Precise measurement of the maximum diameter aids early recognition of tumor regression/growth.

Figure 3. 3D imaging provides accurate definition of the tumor margins, showing microlobulations, tumoral septations, and the spiculations surrounding a tumor. The image at lower left shows a tumor diameter of 2.2 mm measured in the coronal plane. This was larger than previously thought, and the patient is now being considered for neoadjuvant therapy.
Recent refinements in sonographic techniques have yielded harmonic imaging, which in turn improves signal-to-noise ratio. Coupled with the use of microbubbles, which can be used intravenously, microvascularity, namely the capillaries within tissue, can be imaged. Years of research with microbubbles in animal models have shown that the transit time of microbubbles in tumor neovascularity differs significantly from that in normal tissues [6]. In addition, tumors tend to have greater vascular volumes and longer washout times. This is reflected as increased area under the curve (AUC) of a time/intensity plot and longer T1/2 in washout phase.

The CE-TVS differs from standard transvaginal sonography in that its inclusion of intravenous injection of ultrasound contrast with a three-minute recording of time intensity curve and its offline analysis. Microbubbles are prepared by shaking for 45 seconds in a specially designed vial oscillator. After an antecubital intravenous line is placed, 3 µL/kg of Definity® (Lantheus Medical Imaging, N Bellerica, MA) is injected through the intravenous line followed by 10 cc saline flush. Pulse inversion harmonics (PIH) affords depiction of the microbubbles.

Standard transvaginal sonography with a C8-4v transvaginal probe on an iU22 Philips ultrasound scanner (Philips Healthcare, Bothell, WA) is used to image the ovary with color Doppler sonography for detection of vascular areas. Once the location of vascularized areas is determined, contrast injection is performed with split screen images using fundamental and harmonic imaging. Maximum intensity projection (MIP) images called the MicroVascular image (MVI) offer an early detection of ovarian cancer.
Clinical advantages

Color Doppler sonography has been used for many years to distinguish between benign and malignant ovarian masses. The relative resistance to flow is determined for selected vessels and is used to distinguish between abnormal vascular compositions from benign lesions. This is a reflection of numerous arteriovenous shunts and

(Philips Healthcare, Bothell, WA) can be reconstructed offline to aid the quantification region of interest (ROI) placement.

Once a region of interest is chosen, QLAB (Philips Healthcare, Bothell, WA) an off-line software program can determine uptake time, peak enhancement, contrast washout and area under contrast enhancement curve.
decreased vascular tone in tumor vessels. However, the vessel impedance values were seen to overlap between benign and malignant ovarian masses.

Contrast enhanced transvaginal sonography (CE-TVS) is based on the depiction of tumor capillary networks. Clearly, there are differences in the orderly branching and tapering vessels in normal tissues and the chaotic branching and vessel caliber of tumor vessels. This is reflected by increased mean transit times.

Figures 1-6 show the CE-TVS in benign and malignant ovarian tumors. Although both lesions had morphologic features suggestive of malignancy, there were significant differences in their contrast enhancement kinetics.

Figure 3. Mature cystic teratoma (benign): pre-contrast gray scale image (top right image) demonstrated a solid right adnexal mass. Peak enhancement PIH (top left image) images show moderate level of vascularity within the mural thickening. The PIH time-intensity curve of right ovary (bottom image) showed very low peak intensity (5 dB), long half washout time (129 sec) and moderate AUC (499 sec\(^{-1}\)).

Figure 4a. Bilateral serous adenocarcinoma (malignant).
Potential applications

The relatively low incidence (33 per 100,000 in USA) at age 55 and lack of clearly definable risk factors make screening for ovarian cancer a challenge. The fact that less than ten percent of patients ultimately found to have ovarian cancer have a traceable risk factor makes screening a significantly difficult challenge for clinicians.

Our recently published data involving 23 masses showed a twofold difference between peak enhancement, threefold difference in washout time, and almost fourfold difference in vascular volume in malignant ovarian tumors when compared to benign. The time to peak, however, was not statistically, significantly different. Figure 7 show this data in statistical terms, with the statistical averages and standard error.
proteomics. If such a serum test becomes available, contrast-enhanced sonography would be clearly indicated as a secondary test as a means to confirm the presence of ovarian cancer and perhaps assess its extent.

However, without the availability of such a serum screen test, contrast enhanced transvaginal sonography serves to have an even greater role. Clearly, in women with risk factors such as BRCA positive or familial history of breast, ovarian, or endometrial cancer, these women deserve special attention for screening in the hope of early detection.

Another very promising method for early detection of ovarian cancer involves mass spectroscopy of serum protein and gene products, so called proteomics. If such a serum test becomes available, contrast-enhanced sonography would be clearly indicated as a secondary test as a means to confirm the presence of ovarian cancer and perhaps assess its extent.

***Figure 5. Endometrioid adenocarcinoma (malignant).***

Pre-contrast gray scale image (top right image) demonstrates a solid heterogeneous adnexal mass. Peak enhancement PIH (top left image) show extensive vascularity within tumor. The PIH time-intensity curve (bottom image) of right adnexa showed relatively high peak intensity (14 dB), moderate half washout time (45 sec) and elevated AUC (793 sec$^{-1}$).

***Figure 6. Metastatic breast cancer.***

Pre-contrast gray scale image (top right image) demonstrates a large solid irregular adnexal mass. Peak enhancement PIH (top left image) show extensive vascularity within tumor. The PIH time-intensity curve (bottom image) of left adnexa showed high peak intensity (20 dB), prolonged half washout time (81 sec) and elevated AUC (1750 sec$^{-1}$).

With fewer than 10% of patients having a traceable risk factor, screening is difficult.
in detecting early stage ovarian cancer. These screening strategies are currently being tested in several trials. Because of the inherent low prevalence of ovarian cancer, it will take years of testing in multicentered trials to conclusively show efficacy. In any event, the use of CE-TVS seems to be quite promising as a means to detect ovarian cancer in its earliest stages.

**Summary**

CE-TVS is a new technique that seems to be quite accurate in sonographic detection of early stage of ovarian cancer. Its clinical use is currently under investigation in several centers worldwide. It is hoped that this technique can be an effective means to detect early stage ovarian cancer alone or combined with serum testing.

**Acknowledgment**

Figures 1, 4 are reproduced from Reference 1 with permission from the Journal of Ultrasound in Medicine.

### References


