 Recent studies from several medical centers worldwide have shown that contrast enhanced transvaginal sonography (CE-TVS) can detect early stage ovarian cancer. [1, 2, 3, 4]. This major improvement in sonographic detection of tumor microvascular neovascularity has resulted from refinements in sonographic equipment as well as microbubble technology. This overview describes the breakthrough in sonographic techniques that affords early detection of ovarian cancer and a potential use in screening for this “silent killer.”

Clinical Aspects

This year, there will be an estimated 24,000 new cases of ovarian cancer diagnosed and 14,300 deaths in the United States. The incidence of ovarian cancer has been steadily increasing over the past 10 years, with an overall lifetime risk of 1.8% [5]. Despite improvements in median survival through surgical advances and new chemotherapeutic regimens, the overall 5-year survival for women with stage III/IV epithelial ovarian cancer has remained relatively unchanged (15%) over the past 40 years [5].

In contrast, women diagnosed with disease confined to the ovary (stage I), require less morbid surgical intervention, may not require adjuvant chemotherapy, have a significantly improved quality of life, and most importantly have an overall 5-year survival approximating 90%.

Unfortunately, 75% of women continue to be diagnosed with advanced stage disease, which is ample evidence of the inadequacy of a pelvic examination and standard sonography. Therefore, the detection of early stage epithelial ovarian cancer is thought to be the most efficient means to improve survival until the development of an effective therapy.

Instrumentation and technique

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)
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.

Figure 1. Endometrioma (benign): Pre-contrast gray scale images (top right image) demonstrate a cystic left adnexal mass with irregular mural thickening. Each enhancement PIH (top left image) image shows moderate level of vascularity within lesions wall. The Pulse Inversion Harmonics (PIH) time-intensity curve of right ovary (bottom image) showed moderate peak intensity (17 dB), short half washout time (68 sec) and moderately increased Area Under Curve (AUC) (1085 sec⁻¹).

Figure 2. Mucinous cystadenoma (benign): pre-contrast gray scale image (top right image) demonstrated a cystic left adnexal mass with irregular thickened wall. Peak enhancement PIH (top left image) images show low level of vascularity within the mural thickening. The PIH time-intensity curve of right ovary (bottom image) showed moderate peak intensity (17 dB), short half washout time (23 sec) and low AUC (322 sec⁻¹).
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.
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.

**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.
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.

However, without the availability of such a serum screen test, contrast enhanced transvaginal sonography serves to have an even greater role.
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


