Ovarian & Endometrial Cancer
Introduction

Early detection of gynecological cancers can be the difference between life and death. At Garden OB/GYN, we are able to detect ovarian and endometrial cancer at an earlier stage than other OBGYN practices. Thanks to our expertise in 3D and Doppler ultrasound, we are able to thoroughly examine our patients in the office, at every visit. Patient survival rates improve drastically with a prompt diagnosis.

“Transvaginal ultrasound is effective in the detection of ovarian cancer and should be a routine test as part of annual examinations for women, report the Society of Gynecological Oncologist researchers.”  
-Cancer, American Cancer Society

“International Federation of Gynecology and Obstetrics Stage I ovarian carcinoma, which has the worst prognosis among all types of gynecologic carcinoma, has a high cure rate as has been reported, but early diagnosis is difficult and to the authors’ knowledge screening methods have not been established. Since 1989, the authors have performed transvaginal ultrasonography (TVS) as a form of screening for ovarian carcinoma.” “These results are significant in that 77.3% of the primary ovarian carcinomas found during the current screening were of curable Stage I. Increased use of TVS screening for ovarian carcinoma may increase the chance for early diagnosis and decrease the mortality of the disease.”

- American Cancer Society, 2000 – Presented at the 15th World Congress of Gynecology and Obstetrics

“A number of imaging methods have been evaluated for possible use in ovarian cancer screening. Transvaginal ultrasound has consistently proven to be the most promising imaging method for routine screening of ovarian cancer.”

-Memorial Sloan Kettering Cancer Center
“Ultrasound and Doppler are being widely studied for their potential to screen for ovarian and endometrial cancer to increase early detection and should be considered as a part of the annual gynecological visit.”

“The results reported in recent literature on three dimensional color power Doppler are indeed provocative and, not surprisingly, raise many questions about the regulation of tumor angiogenesis, the density of tumor vessels and the differences between vessel architecture in benign and malignant growths. Three dimensional power Doppler depictions of tumor angiogenesis has many clinical implications including the early detection of ovarian and endometrial cancers. Improved detection and classification of tumor architecture may contribute to better diagnostic accuracy and consequently to a reduction in morbidity and mortality from these two cancers.”

According to the editor in chief of Contemporary OB/GYN, Dr. Charles Lockwood, the use of vaginal ultrasound as part of a routine gynecological examination, has been advocated by many physicians for many years, including the leading pioneer in Gynecology, Dr. Steven Goldstein at New York University.
At Garden OB/GYN, we firmly believe that annual transvaginal sonogram is an important screening that should be offered to all women at the time of their well woman check-up. What sets us apart from other practices is our pro active care that focuses on a woman's health by taking preventative measures. Baseline ultrasound with yearly follow up can detect tissue changes in the early stages of cancer before symptoms surface. Once a woman is developing symptoms it may be too late. Why wait? If ovarian cancer is found at Stage 1, there is a 75% chance for survival. Once a patient is at Stage 4, death is imminent. We hypothesize that by screening the asymptomatic patient on a yearly basis will astronomically decrease gynecological cancer fatality.

Garden OB/GYN is an AIUM Accredited practice. All offices are equipped with high end sonogram machines and are operated by expert ultrasonogram technicians, trained specifically in OB/GYN. Our state of the art facility uses cutting edge technology such as 3D reconstruction, multiplane, tomographic ultrasound imaging and Doppler studies to provide precise pelvic anatomy assessment.

Three-dimensional ultrasound offers two advances over conventional ultrasound, improved spatial orientation in association with surface rendering and objective quantification of an organs volume and blood flow.
“Transvaginal color Doppler sonography is capable of detecting ovarian carcinoma as early as stage 1. Furthermore, it has proved its potential in detecting the disease in asymptomatic women as well as in women with normal sized ovaries. These results could justify its use as a routine test in annual check-ups. Its use would be particularly justified in women at high risk.”

In the United States, a woman is diagnosed with a gynecologic cancer every 7 minutes totaling almost 95,000 new cases each year and each year, approximately 28,500 women will die due to gynecological cancer. One unfortunate fact about GYN cancers is that many are diagnosed when the grade and stage have advanced resulting in slim chances for survival. With annual sonograms, a patient’s future is more promising thanks to early detection yielding a more positive prognosis.

Symptoms can vary based on the type of cancer (Chart 2). Early stages are typically asymptomatic. One surprising, yet frightening fact is ovarian cancer symptoms mimic benign conditions such as bloating, menstrual changes, upset stomach, and fatigue. When symptoms start to present, it will unfortunately usually indicate progression of the cancer.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Cervical Cancer</th>
<th>Ovarian Cancer</th>
<th>Uterine Cancer</th>
<th>Vaginal Cancer</th>
<th>Vulvar Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal vaginal bleeding or discharge</td>
<td>☒</td>
<td>☐</td>
<td>☒</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Pelvic pain or pressure</td>
<td>☐</td>
<td>☒</td>
<td>☒</td>
<td>☒</td>
<td>☐</td>
</tr>
<tr>
<td>Abdominal or back pain</td>
<td>☐</td>
<td>☐</td>
<td>☒</td>
<td>☒</td>
<td>☐</td>
</tr>
<tr>
<td>Bloating</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Changes in bathroom habits</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Itching or burning of the vulva</td>
<td>☐</td>
<td>☒</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Changes in vulva color or skin, such as a rash, sores, or warts</td>
<td>☐</td>
<td>☒</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

Chart 2

Statistics: Source, American Cancer Society 2014

<table>
<thead>
<tr>
<th>Cancer</th>
<th>New Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical</td>
<td>12,360</td>
<td>4,020</td>
</tr>
<tr>
<td>Ovarian</td>
<td>21,980</td>
<td>14,270</td>
</tr>
<tr>
<td>Uterine</td>
<td>52,630</td>
<td>8,590</td>
</tr>
<tr>
<td>Vaginal</td>
<td>3,170</td>
<td>880</td>
</tr>
<tr>
<td>Vulvar</td>
<td>4,850</td>
<td>1,030</td>
</tr>
<tr>
<td>TOTAL</td>
<td>94,990</td>
<td>28,103</td>
</tr>
</tbody>
</table>

Chart 1
Gynecologic cancers include ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, vulvar cancer, and cancer of the fallopian tubes (Image 1):

While uterine cancer is the most common GYN cancer with more than 52,500 new cases a year, ovarian cancer is the deadliest due to late stage diagnosis.
Ovarian cancer is the leading cause of death from gynecologic cancers and the 5th leading cause of death among women. American Cancer Society estimates 22,280 women will be diagnosed with ovarian cancer in the United States in 2012 and about 15,500 women will die from the disease. All women are at risk for ovarian cancer.

Not all gynecological cancers can be prevented however; early diagnosis is possible with Annual GYN exams, annual transvaginal sonogram with Doppler’s, and tumor marker serology. Ultrasound examination can help classify benign or malignant adnexal tumors. Malignancy can be classified by using the following 5 rules:

1) Irregular solid tumor
2) Ascites
3) At least 4 papillary structures
4) Irregular multilocular-solid tumor with largest diameter of 100mm
5) Very high color content on color Doppler examination

The 5 signs suggesting a benign mass are:
1) Unilocular cyst
2) Presence of solid components where the largest component is <7mm in the largest diameter
3) Acoustic shadows
4) Smooth multilocular tumor less than 100mm in the largest diameter
5) No detectable blood flow on Doppler examination

By utilizing ultrasound, the above markers help clinicians visualize the pelvis and provide insight to what may otherwise be missed on a simple bi-manual exam. With performing ultrasound on annual well woman exams, it makes it possible to catch changes earlier with a higher hope for faster treatment with promising patient outcomes. Although ovarian cancer has a poor prognosis, early detection has a much higher cure rate.

Survival Rates by Stage of Diagnosis

<table>
<thead>
<tr>
<th>FIGO Stage</th>
<th>Proportion of Cases (%)</th>
<th>5-Year Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>19.3</td>
<td>92.1</td>
</tr>
<tr>
<td>1b</td>
<td>2.7</td>
<td>84.9</td>
</tr>
<tr>
<td>1c</td>
<td>8.1</td>
<td>82.4</td>
</tr>
<tr>
<td>2a</td>
<td>2.7</td>
<td>59.0</td>
</tr>
<tr>
<td>2b</td>
<td>4.2</td>
<td>55.4</td>
</tr>
<tr>
<td>2c</td>
<td>3.0</td>
<td>51.4</td>
</tr>
<tr>
<td>3a</td>
<td>5.9</td>
<td>39.3</td>
</tr>
<tr>
<td>3b</td>
<td>8.6</td>
<td>25.5</td>
</tr>
<tr>
<td>3c</td>
<td>13.0</td>
<td>17.1</td>
</tr>
<tr>
<td>4</td>
<td>28.3</td>
<td>11.6</td>
</tr>
</tbody>
</table>
Survival Statistics

Based on data from SEER 18 2005–2011. Gray figures represent those who have died from ovary cancer. Green figures represent those who have survived 5 years or more.
Endometrial & Uterine Cancer

At Garden OB/GYN, endometrial cancers are found more frequently in the early stages thanks to transvaginal ultrasound. With early detection, patients have more than a 95% chance for survival. In comparison to other OB/GYN practices which do not perform annual sonography, diagnosis will occur when the patients start to bleed, indicating that the cancer has progressed and spread. This may be late stage of endometrial cancer and the survival for these patients will be less than 10%.

Uterine cancer is the most common of all GYN cancers with over 50,000 newly diagnosed cases each year. Early detection can be made possible with routine annual sonography. Typically, uterine cancer occurs after menopause however, it can occur in younger women as well. Certain factors predispose women to endometrial cancer such as obesity, null parity, patients with history of tamoxifen treatment, and women who are on estrogen hormonal replacement therapy.

Symptoms of uterine cancer include:

- Vaginal bleeding after menopause
- Bleeding between periods
- An abnormal, watery or blood-tinged discharge from your vagina
- Pelvic pain
- Pain during intercourse

The key in diagnosis of uterine cancer, as in all cancers, is early diagnosis. As in other GYN cancers, annual transvaginal ultrasound can provide an image of the uterine lining. Obtaining images on a yearly basis ensures the patients have through assessments performed. When a bi-manual pelvic exam is performed, there is no way for a clinician to palpate changes occurring inside the uterus. When uterine lining abnormalities are visualized by ultrasound, it provides the alarm to further investigate the changes – by performing Hysteroscopy we can visualize the interior of the uterus and with Dilation and
Curettage, a sample of the uterine lining is obtained which will provide a definitive diagnosis for the changes noted initially.

**Uterine Cancer Staging**

- **Stage I** cancer is found only in your uterus.
- **Stage II** cancer is present in both the uterus and cervix.
- **Stage III** cancer has spread beyond the uterus, but hasn’t reached the rectum and bladder. The pelvic area lymph nodes may be involved.
- **Stage IV** cancer has spread past the pelvic region and can affect the bladder, rectum and more-distant parts of your body.

**Endometrial and Uterine Cancer Incidence, by Race/Ethnicity and Age, 2000–2005**

*Source: NCI* [National Cancer Institute, Surveillance, Epidemiology, and End Results (SEER) Program](https://seer.cancer.gov/)

![Graph showing incidence by race/ethnicity and age](image)

*Totals include females of all ages. **May include Hispanics.*

**Endometrial and Uterine Cancer Survival Rates**

**Five-year Period Survival Rates for Ovarian Cancer, by Race and Stage,** 1996–2004

*Source: NCI, National Cancer Institute, Surveillance, Epidemiology, and End Results (SEER) Program*

![Graph showing survival rates by stage](image)

*Includes races and ethnicities other than White and Black. **Localized cancer is limited to the organ in which it began (no evidence of spread); regional cancer has spread beyond the primary site, but not to distant organs or lymph nodes; and unstaged indicates that there was not enough information to determine a stage.*
Cancer Cost

As the US population grows and age increases, so do cancer expenditures. According to NIH, cancer costs are projected to reach at least $158 billion in 2020.\(^{14}\)

Annual sonogram can prevent all costs listed below, save a life, and can save a family from unnecessary pain and suffering.

When considering the cost of Cancer, many initially start to think of expensive medications and frequent visits with their healthcare providers. Many may overlook other hidden expenses associated with cancer treatment and the consequence an individual will inevitably need to face. Potential costs can leave a patient and their family feeling overwhelmed and anxious. Common financial categories for cancer care include:
Ovarian Cancer is one of the most expensive cancers to treat.

Chemotherapy for ovarian cancer is made from platinum derivatives (Cisplatin & Carboplatin) therefore, every treatment is about $30,000. Patients will need treatment with these chemotherapy medications 3 times per week for years, or as long as they survive. This therapy alone may cost $4 - $5 million per year.

A real patient testimonial from Naples, Florida, according to chemotherapycost.com:

**Treatment for metastatic ovarian cancer**

**Amount:** $1,072.82 *not covered by insurance*  
**Type of Cancer:** Ovarian  
**Drugs Used:** Avastin  
**Method of Administration:** infusion  
**Provider:** Infusion center

**Patient Comments:** Recently diagnosed with metastatic ovarian cancer. Drugs being administered are Avastin, Gemzar and Carboplatin. The most recent statement has the original cost of one session at $30,045.79. Health paid $2,503 and I will pay 1,072.
References


Supporting Articles


John R. van Nagell, Jr, MD; Paul D. DePriest, MD; Frederick R. Ueland, MD; Christopher P. DeSimone, MD; Amy L. Cooper, MD; J. Matt McDonald, MD; Edward J. Pavlik, PhD; Richard J. Kryscio, PhD. “Ovarian Cancer Screening With Annual Transvaginal Sonography. Findings of 25,000 Women Screened”. January 16, 2007. Retrieved April 19, 2015. http://www.researchgate.net/publication/6433063_Ovarian_cancer_screening_with_annual_transvaginal_sonography_findings_of_25000_women_screened

Transvaginal Ultrasound Detects Early Ovarian Cancer and May Improve the Chance for Cure

Transvaginal ultrasound is effective in the detection of ovarian cancer and should be a routine test as part of annual examinations for women, report the Society of Gynecological Oncologist researchers. Every woman 50 years or older or age 30 with a family history of ovarian cancer is at a higher risk of getting ovarian cancer. The earlier ovarian cancer is detected, the higher the cure rate. Unfortunately, most cases of ovarian cancer are diagnosed at an advanced stage, meaning the cancer has spread from the ovaries to other parts of the body, and is often incurable.

Cancer of the ovary, or ovarian cancer, is a common malignancy occurring in women in the United States with about 25,000 new cases diagnosed each year. The ovaries are small female reproductive organs that reside in the pelvis. The ovary makes female hormones and stores all of the egg cells which are released once a month during ovulation. There are two ovaries, one on each side of the uterus, or womb. The most frequent cancerous ovarian tumors originate from the cells in the lining, or epithelium of the ovary and are collectively referred to as epithelial cancers of the ovaries. Cancers may also originate from germ cells in the ovary (cells that are destined to form eggs), or sex cord stromal cells (cells that secrete hormones and connect the different structures of the ovaries). Because ovarian cancers begin deep in the pelvis, they often do not cause any symptoms until they are at an advanced stage. At the time of initial diagnosis, the majority of women have advanced cancer. Currently, very few women with advanced ovarian cancer are cured. In order to improve outcomes for women with ovarian cancer the disease has to be diagnosed early, before it spreads.

Two groups of researchers have reported that transvaginal ultrasound is an effective and rapid screening technique for detecting ovarian cancer. Transvaginal ultrasound works by transmitting sound waves that bounce off structures in the body to a receiver. A picture of the internal structures is created which the physician can visualize to detect any abnormalities. Because cancerous tumors are a different density than normal tissue in the body, the sound waves create a different pattern when they bounce off the tumor and can be detected on the picture created. When the receiver of sound waves is placed in the vagina (transvaginal), small cancers of the ovary can be detected. In addition to effective screening, this test is painless and only adds one to 5 minutes to the usual pelvic examination.

Two separate studies involving almost two hundred thousand healthy women evaluated the use of transvaginal sonography as a part of annual examinations. In both studies, transvaginal sonography detected stage I and II ovarian cancer in many women, dramatically increasing chances for a cure. These early stage cancers probably would not have been detected by a normal pelvic examination. Advanced stage ovarian cancers were also detected through this technique. (31st annual meeting of the Society of Gynecologic Oncologists, February, 2000).

It appears from these two studies that transvaginal sonography should be a part of the annual examination for all women over the age of 50 and those at high risk for developing ovarian cancer, in order to detect the cancer in a curable stage. Women that are over 50 or at high risk for ovarian cancer should talk with their doctor about including transvaginal ultrasound as part of their annual examination. (Cancer, Vol 89, No3, pp 582-587, 2000)
Usefulness of Mass Screening for Ovarian Carcinoma Using Transvaginal Ultrasonography

Shigemi Sato, M.D.
Yoshihito Yokoyama, M.D.
Tomomi Sakamoto, M.D.
Masayuki Futagami, M.D.
Yoshiharu Saito, M.D.

Department of Obstetrics and Gynecology, Hirosaki University School of Medicine, Hirosaki, Japan.
Presented in part at the 15th World Congress of Gynecology and Obstetrics (FIGO), Copenhagen, Denmark, August 3–8, 1997.
Address for reprints: Shigemi Sato, M.D., Department of Obstetrics and Gynecology, Hirosaki University School of Medicine, 5, Zaifu-chou, Hirosaki, 036-8256, Japan.
Received August 23, 1999; revisions received January 3, 2000, and March 30, 2000; accepted March 30, 2000.

BACKGROUND. International Federation of Gynecology and Obstetrics Stage I ovarian carcinoma, which has the worst prognosis among all types of gynecologic carcinoma, has a high cure rate as has been reported, but early diagnosis is difficult and to the authors’ knowledge screening methods have not been established. Since 1989, the authors have performed transvaginal ultrasonography (TVS) as a form of screening for ovarian carcinoma. The purpose of the current study was to summarize and evaluate screening results for the last 10 years with respect to ovarian carcinoma diagnosis and risk factors.

METHODS. Primary screening by TVS was performed in asymptomatic women who participated in annual uterine cervical carcinoma screening. Four scanning sections by TVS were established and all sonograms were recorded. Women with abnormal sonograms (a mass $\geq 30$ mm in greatest dimension or a mass with a mixed pattern) received secondary screening and closer examination with a tumor marker and an imaging diagnostic examination. Laparotomy was conducted on all masses with a greatest dimension of $\geq 60$ mm or on suspected malignant masses. Subject information-related risk factors also were recorded.

RESULTS. Subjects were 183,034 women who participated in primary screening. Of these women, 51,550 were undergoing screening for the first time. The time required for primary screening was 1 minute per subject. Secondary screening was required for 5309 participants (10.3%) and surgery was performed on 324 participants. Twenty-two primary tumors and 2 metastatic tumors were detected for a diagnostic rate of 0.047%. Of the 22 primary tumors, 17 (77.3%) were classified as Stage I carcinoma, with tumor markers positive only for 5 (29.4%). The percentage of the total number of Stage I ovarian carcinoma cases increased after the induction of screening from 29.7% to 58.8%.

CONCLUSIONS. These results are significant in that 77.3% of the primary ovarian carcinomas found during the current screening were of curable Stage I. Increased use of TVS screening for ovarian carcinoma may increase the chance for early diagnosis and decrease the mortality of the disease. Cancer 2000;89:582–8.
Ovarian carcinoma is a gynecologic malignancy that carries the poorest prognosis. Its early diagnosis and treatment may be important in improving patient prognosis because favorable results for the treatment of early stages of ovarian carcinoma recently have been demonstrated. The early diagnosis of ovarian carcinoma is more difficult than that of uterine cervical or endometrial carcinoma, and to our knowledge screening for ovarian carcinoma has not been standardized. Screening for ovarian carcinoma includes tumor marker measurement and ultrasonography. Since 1989, we have used transvaginal ultrasonography (TVS) as a form of screening for ovarian carcinoma in asymptomatic women that living in Aomori Prefecture and participating in annual uterine cervical carcinoma screening provided under the auspices of the Health and Medical Service Law for the Aged. In the current study the prospective results of TVS mass screening over the course of 10 years were summarized and analyzed to ascertain the effect of the screening on the prognosis for patients with ovarian carcinoma based on the results of treatment in our department.

**MATERIALS AND METHODS**

**Screening Program**

Screening is comprised of primary and secondary screenings and closer examination, similar to screening for uterine cervical carcinoma. The screening program using TVS is shown in Figure 1. For primary screening, TVS was used in asymptomatic women age > 30 years who lived Aomori Prefecture and underwent annual uterine cervical carcinoma screening provided under the auspices of the Health and Medical Service Law for the Aged.

This screening program was explained to the women participating and their informed consent was obtained.
Primary Screening
Primary screening was performed at the same time as screening for uterine cervical carcinoma. After the collection of a cervical Papanicolaou smears and completion of a bimanual pelvic examination, scanning by TVS was performed on the small pelvic cavity with a 5-megahertz transducer connected to a Sonovista-SL MEU 1577 ultrasound unit (Mochida Pharmaceutical Co., Ltd., Tokyo, Japan). To shorten the time required for examination and to obtain the same conditions during primary screening, four scanning sections for TVS were established. In the first section, uterine longitudinal section was visualized, with left and right sections at 45° (the second and third section) and a section at 90° (the fourth section), which served to divide the pelvic cavity into 8 portions from the caudal side. This method allowed a mass with a long axis of ≥ 30 mm to be scanned in any of sections. Images were recorded using an 8-mm videotape recorder to shorten the time required for examination and to allow archiving and analysis of findings.

Secondary Screening
Secondary screening was considered necessary if a mass with a long axis of ≥ 30 mm was noted in the pelvic cavity, including the intact tissue of the ovaries; if a mass showed a mixed pattern, regardless of tumor size; and/or when ascites measuring ≥ 50 mm were found in the rectouterine pouch. Secondary screening included transvaginal reultrasonography and measurement of tumor markers (CA 125, CA 19-9, carcinoembryonic antigen, α-fetoprotein, and lactate dehydrogenase fraction 5) for ovarian carcinoma.

Closer Examination
Closer examination was considered necessary if a mass with a long axis of ≥ 30 mm was found, a mass showed a mixed echographic pattern, and/or if the tumor marker was positive. Closer examination included radiologic examination such as computed tomography, magnetic resonance imaging, and tumor marker remeasurement within 1 month.

Surgery and Follow-Up
Laparotomy for the surgical removal of a mass and pathologic examination were conducted if a mass with a long axis of ≥ 60 mm was found; if a mass showed a mixed pattern, regardless of tumor size; and/or if the tumor marker again was positive. For a mass with a long axis of ≤ 60 mm but with no mixed pattern, TVS was conducted every 1–3 months to follow the mass. If secondary screening revealed a mass that appeared to be a mature ovarian follicle, the mass was classified as a functional cyst and TVS was conducted yearly.

Treatment
Excised ovarian tumors were examined microscopically and classified histologically according to the World Health Organization classification system. Ovarian tumors were staged according to the International Federation of Gynecology and Obstetrics (FIGO) staging system of 1988 and patients were treated with cisplatin-based chemotherapy after surgery except for those with tumors of borderline malignancy.

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Distribution in the Screened Women</td>
</tr>
<tr>
<td>Age (yrs)</td>
</tr>
<tr>
<td>No.</td>
</tr>
<tr>
<td>No. Personal history of cancer</td>
</tr>
</tbody>
</table>
Determination of Risk Factors for Ovarian Carcinoma

Of 122 patients treated in our department after 1981 who were diagnosed histopathologically with ovarian carcinoma or an ovarian tumor of borderline malignancy, 101 patients who could be followed were included in the ovarian carcinoma group. The control group was comprised of 220 women who visited the department with symptoms and were diagnosed with no abnormalities. Those women with a past history of malignant tumors or cervical or ovarian disease were excluded from the control group. Items for evaluation included age, family history of cancer, past medical history, complications, obesity, pregnancy and labor, and infertility and infertility treatment; data regarding menstruation for both groups was subjected to a chi-square test using contingency tables and multiple regression analysis. Stat View for Macintosh, version 5.0 (SAS Institute, Inc., Cary, NC), was used as the software analysis.

RESULTS

Screening Results

The age distribution for the screened women and their personal histories of cancer are shown in Table 1. Subjects were identified as 24,950 (48.4%) and 26,600 (51.6%) premenopausal and postmenopausal women, respectively. Of the premenopausal women, 37 (0.15%) had a personal history of cancer, whereas 217 of the postmenopausal women (0.81%) had such a history. Results of ovarian carcinoma screening are summarized as shown in Figure 2. A total of 183,034 women participated in primary screening, and participants who underwent the primary screening repeatedly also were included. Of these women, 51,550 took part in screening for the first time. The time required for the primary screening was approximately 1 minute per subject, including uterine cervical carcinoma screening and ovarian carcinoma screening. The time required for scanning by a transvaginal probe was only 30 seconds per subject. Secondary screening was required for 5309 (or 2.9%) of all participants, and 10.3% of the first-time participants. Only 4452 of the 5309 women assessed as requiring secondary screening (83.9%) underwent the secondary screening.
Closer examination was required for 2554 (or 57.4%) of the 4452 women who participated in secondary screening. Laparotomy was conducted in 320 of the 4452 participants from the secondary screening (7.2%), and 4 of the 46,241 were assessed as requiring no secondary screening while undergoing primary screening. Twenty-two patients were diagnosed with primary ovarian carcinoma and 2 patients were diagnosed with metastatic ovarian carcinoma. The diagnostic rate of ovarian carcinoma was 0.013% for all participants (1/7700) and 0.045% for the first-time participants (1/2200). Of the 22 patients with primary ovarian carcinoma, 14 were first-time participants, 4 were followed with TVS every 1–3 months, and 4 were assessed as needing no secondary screening while undergoing primary screening. These last eight patients were diagnosed with pathologic Stage I disease (Table 2). Of the 22 primary tumors, 17 (77.3%) (including 4 borderline tumors) were classified as Stage I disease, 2 were classified as Stage II disease, 2 were classified as Stage III disease, and 1 was classified as Stage IV disease (Table 2). At last follow-up all the patients diagnosed with Stage I disease, including those with borderline malignancy, were alive and well with no evidence of recurrence, a finding we believe was a result of screening. The tumor marker was positive in 10 of the 22 primary tumors (45.5%), but positive in only 5 of the 17 Stage I tumors (29.4%) (Table 2). Half of the 22 primary tumors had a long axis that was < 60mm and were not palpable during the pelvic examination during screening (Table 2). With the closer examination, 21 of the 22 primary tumors were found to show a mixed pattern with no common histopathologic characteristics (Table 2). The diagnosis of 300 patients with benign ovarian tumors of the 324 patients who underwent laparotomy included tumors that were determined to be a dermoid cyst (44.3%), a serous cystadenoma (20.0%), an endometrial cyst (15.3%), a mucinous cystadenoma (12.0%), and other types (8.4%) (Table 3). Other types included 15 paraovarian cysts, 7 simple cysts, 2 follicular cysts, and 1 corpus luteum cyst. There was no false-positive diagnosis. Participants in the screening are registered in a computer system and various data were collected to detect false-negative cases. No ovarian carcinoma cases were diagnosed in participants not undergoing the secondary screening or those who were not followed with ultrasonography. Two patients were falsely assessed as requiring no secondary screening by primary screening 3 months earlier.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yrs)</th>
<th>Detection time</th>
<th>Sonographic findings</th>
<th>Tumor size (mm)</th>
<th>Pelvic examination</th>
<th>Tumor marker</th>
<th>Clinical stage</th>
<th>Histologic type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>First time</td>
<td>Mixed</td>
<td>48</td>
<td>Not palpable</td>
<td>Negative</td>
<td>IB</td>
<td>Mucinous, LPM</td>
</tr>
<tr>
<td>2</td>
<td>62</td>
<td>First time</td>
<td>Mixed</td>
<td>88</td>
<td>Palpable</td>
<td>Positive</td>
<td>IC</td>
<td>Mucinous</td>
</tr>
<tr>
<td>3</td>
<td>43</td>
<td>First time</td>
<td>Mixed</td>
<td>110</td>
<td>Palpable</td>
<td>Negative</td>
<td>IA</td>
<td>Granulosa cell</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>First time</td>
<td>Mixed</td>
<td>22</td>
<td>Not palpable</td>
<td>Positive</td>
<td>IA</td>
<td>Endometrioid</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>First time</td>
<td>Mixed</td>
<td>54</td>
<td>Not palpable</td>
<td>Negative</td>
<td>IA</td>
<td>Serous</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>First time</td>
<td>Mixed</td>
<td>56</td>
<td>Not palpable</td>
<td>Positive</td>
<td>IA</td>
<td>Mucinous</td>
</tr>
<tr>
<td>7</td>
<td>45</td>
<td>First time</td>
<td>Mixed</td>
<td>87</td>
<td>Palpable</td>
<td>Negative</td>
<td>IC</td>
<td>Mucinous</td>
</tr>
<tr>
<td>8</td>
<td>59</td>
<td>First time</td>
<td>Mixed</td>
<td>52</td>
<td>Not palpable</td>
<td>Positive</td>
<td>IC</td>
<td>Clear cell</td>
</tr>
<tr>
<td>9</td>
<td>50</td>
<td>First time</td>
<td>Mixed</td>
<td>65</td>
<td>Palpable</td>
<td>Negative</td>
<td>IC</td>
<td>Mucinous</td>
</tr>
<tr>
<td>10</td>
<td>53</td>
<td>Follow-up</td>
<td>Mixed</td>
<td>71</td>
<td>Not palpable</td>
<td>Negative</td>
<td>IA</td>
<td>Serous, LPM</td>
</tr>
<tr>
<td>11</td>
<td>43</td>
<td>Follow-up</td>
<td>Mixed</td>
<td>41</td>
<td>Not palpable</td>
<td>Negative</td>
<td>IC</td>
<td>Clear cell</td>
</tr>
<tr>
<td>12</td>
<td>54</td>
<td>Follow-up</td>
<td>Mixed</td>
<td>55</td>
<td>Not palpable</td>
<td>Positive</td>
<td>IC</td>
<td>Mucinous, LPM</td>
</tr>
<tr>
<td>13</td>
<td>61</td>
<td>Follow-up</td>
<td>Cystic</td>
<td>60</td>
<td>Not palpable</td>
<td>Negative</td>
<td>IC</td>
<td>Endometrioid</td>
</tr>
<tr>
<td>14</td>
<td>53</td>
<td>Repeat</td>
<td>Mixed</td>
<td>48</td>
<td>Not palpable</td>
<td>Positive</td>
<td>IC</td>
<td>Clear cell</td>
</tr>
<tr>
<td>15</td>
<td>60</td>
<td>Repeat</td>
<td>Mixed</td>
<td>46</td>
<td>Not palpable</td>
<td>Positive</td>
<td>IC</td>
<td>Mucinous</td>
</tr>
<tr>
<td>16</td>
<td>40</td>
<td>Repeat</td>
<td>Mixed</td>
<td>34</td>
<td>Not palpable</td>
<td>Negative</td>
<td>IC</td>
<td>Endometrioid</td>
</tr>
<tr>
<td>17</td>
<td>56</td>
<td>Repeat</td>
<td>Mixed</td>
<td>45</td>
<td>Not palpable</td>
<td>Negative</td>
<td>IA</td>
<td>Mucinous</td>
</tr>
<tr>
<td>18</td>
<td>65</td>
<td>First time</td>
<td>Mixed</td>
<td>65</td>
<td>Palpable</td>
<td>Positive</td>
<td>IC</td>
<td>Serous</td>
</tr>
<tr>
<td>19</td>
<td>60</td>
<td>First time</td>
<td>Mixed</td>
<td>84</td>
<td>Palpable</td>
<td>Positive</td>
<td>IC</td>
<td>Mucinous</td>
</tr>
<tr>
<td>20</td>
<td>63</td>
<td>First time</td>
<td>Mixed</td>
<td>70</td>
<td>Palpable</td>
<td>Positive</td>
<td>IC</td>
<td>Serous</td>
</tr>
<tr>
<td>21</td>
<td>67</td>
<td>First time</td>
<td>Mixed</td>
<td>85</td>
<td>Palpable</td>
<td>Positive</td>
<td>IC</td>
<td>Serous</td>
</tr>
<tr>
<td>22</td>
<td>47</td>
<td>First time</td>
<td>Mixed</td>
<td>91</td>
<td>Palpable</td>
<td>Negative</td>
<td>IC</td>
<td>Serous, LPM</td>
</tr>
<tr>
<td>23</td>
<td>49</td>
<td>First time</td>
<td>Mixed</td>
<td>64</td>
<td>Palpable</td>
<td>Negative</td>
<td>Metastasis</td>
<td>Pseudomyxoma</td>
</tr>
<tr>
<td>24</td>
<td>60</td>
<td>First time</td>
<td>Mixed</td>
<td>50</td>
<td>Palpable</td>
<td>Negative</td>
<td>Metastasis</td>
<td>Pseudomyxoma</td>
</tr>
</tbody>
</table>

TVS: transvaginal ultrasonography; LPM: Luteinized.
Clinical Stage before and after the Induction of Screening

The changes in the clinical stage of the patients treated in the department before and after the induction of ovarian carcinoma screening are shown in Table 4. Prior to the induction, the clinical stage was classified as Stage I in 11 patients (29.7%), Stage II in 5 patients (13.5%), Stage III in 16 patients (43.3%), and Stage IV in 5 patients (13.5%). Conversely, after the induction of screening, the clinical stage was classified as Stage I in 50 patients (58.8%), Stage II in 8 patients (9.4%), Stage III in 19 patients (22.4%), and Stage IV in 8 patients (9.4%). In other words, comparison of the clinical stage of these ovarian carcinoma cases before and after the induction of screening indicated that 56% of all cases were Stage III and IV tumors prior to screening induction whereas 58.8% were classified as Stage I tumors thereafter.

Risk Factors for Ovarian Carcinoma

The mean age was 54.5 years for the carcinoma group and 51.4 years for the control group. Single variate analysis using a chi-square test revealed that the carcinoma group had a significantly higher prevalence of breast, endometrial, and pancreatic carcinomas in first-degree and second-degree relatives than the control group. The presence of ovarian carcinoma was found to be correlated significantly with obesity and infertility. There was a nonsignificant but close correlation with an age of ≥ 50 years and nulliparity. Multivariate analysis using a multiple regression model revealed that a family history of breast and endometrial carcinomas and a family history of obesity were independent risk factors (Table 5). Age, infertility, and a family history of pancreatic carcinoma appeared to be significant risk factors. No first-degree or second-degree relatives were found to have ovarian carcinoma in the carcinoma group and only 2 of 220 controls (0.9%) were found to have first-degree or second-degree relatives with ovarian carcinoma; the differences were not statistically significant between the groups.

DISCUSSION

In screening for ovarian carcinoma using TVS, which detects an ovarian mass directly, the time required for examination and diagnostic criteria are the most important factors. The time for examination depends on the method, which in this study involved measuring the long axis of the ovaries using TVS in approximately 30 seconds, a time period that may be suitable for screening. Using the ovarian volume or radiographic findings of a tumor are more time-consuming and may be obstructive. DePriest et al.8 and
van Nagell et al. calculated the volume of the ovaries by TVS during screening for ovarian carcinoma and considered the value abnormal when it exceeded 20 cm³ before menopause and 10 cm³ thereafter. Approximately 1.4% of the screening participants were diagnosed with an abnormality and approximately 0.9% of these individuals were diagnosed with malignancy. To avoid false-negative diagnoses, the current screening method included secondary screening if a tumor with a long axis of $\geq 30$ mm was detected and/or if a tumor showed a mixed pattern, regardless of tumor size (Fig. 1). Conversely, the average length of the long axis of a normal ovary generally is 30 mm for premenopausal women and grows to approximately 40 mm with ovulation. Thus, some benign tumors and functional cysts were included and the abnormality rate was as high as 2.9% for all the participants and 10.3% for first-time participants. Ovarian carcinoma was diagnosed in 0.047% of first-time participants (Fig. 2). We believe the difference in the diagnostic rate of ovarian carcinoma is attributable to the prevalence of the disease among women in the U.S. and Japan. The clinical stage of the primary tumor was Stage I in 77.3% of subjects (Table 2), which may fulfill the aim of early diagnosis. One of the effects of this screening method has been a change in diagnostic results. Comparing the clinical stage of ovarian carcinoma cases, 56% of all cases were classified as Stage III and IV before the introduction of screening whereas 58.8% of all cases were classified as Stage I disease thereafter (Table 4). This most likely was because pelvic examinations were standardized in a similar manner and more cases of asymptomatic, early ovarian carcinoma were found. At last follow-up, all patients diagnosed with Stage I ovarian carcinoma during primary screening were alive and well with no evidence of disease recurrence. Considering the cure rates for patients with Stage I ovarian carcinoma over 10 years, it is a significant finding that 77.3% of primary carcinoma cases were Stage I, including those that were of borderline malignancy. The cure rate of ovarian carcinoma may be increased greatly by early diagnosis and appropriate treatment, which makes mass screening more significant.

Of the 24 patients with ovarian carcinoma, 14 patients with a primary tumor and 2 with metastatic disease (for a total of 16 patients) were first-time participants who were determined to require secondary screening, closer examination, and laparotomy (Table 2). The other 4 patients were first-time participants who were determined to need secondary screening, follow-up every 1–3 months, and laparotomy (Table 2). The remaining four patients were participants undergoing reexamination every year (Table 2). All eight primary tumors detected at follow-up or reexamination were classified as Stage I. Judging from the excellent cure rate
for Stage I carcinoma and because all cases found at follow-up and reexamination were determined to be Stage I, patients determined to need no secondary screening may undergo subsequent screening alone every year.

Tumor marker measurement may serve as a method of screening for ovarian carcinoma. Its greatest advantages are examination by blood collection and fewer burdens. Its disadvantages are its high cost and insufficient sensitivity and specificity, irrespective of the combination of available tumor markers. The most frequently reported tumor marker is CA 125, with what to our knowledge is the largest number of subjects studied using this marker (22,000 asymptomatic women) reported in a study by Jacobs et al.3 They determined the serum CA 125 level and found 41 patients (0.2%) with a level > 30 U/mL, and 11 of 41 patients had ovarian carcinoma (26.8%). Nineteen ovarian carcinomas were found in their study; therefore, CA 125 was negative in 8 ovarian tumors and was positive in 11 of the 19 (57.9%). Other screening methods combining CA 602 and CA 546 performed in 21,805 women revealed that neither of the markers was positive in 2856 women (13.1%) and that only 5 cases of ovarian carcinoma were discovered (0.02%).12 However, only 2 of these 5 patients (40.0%) were determined to have Stage I disease. Similarly, in previous studies using tumor markers for ovarian carcinoma screening, the disease diagnostic rate and the percentage of Stage I tumors were half as high as those in the current study.13,14 This finding was compatible with the results of the current study, in which tumor markers were found to be negative at a rate of 50% for primary tumors and positive at a low rate for early carcinoma (Table 2). It is natural that a combination of various tumor markers may be required for histologically diverse ovarian tumors. This also is a disadvantage of tumor markers when they are used for screening ovarian carcinoma.

One problem of the current study may be that participants in the screening for ovarian carcinoma were already undergoing uterine cervical carcinoma screening. The prevalence of ovarian carcinoma in Japan is between 25–33% that of uterine cervical carcinoma. Thus, it is necessary to limit the number of subjects for more efficient screening. Since 1988, the medical history of 101 patients with ovarian carcinoma and 220 women with no gynecologic disease have been investigated in detail, and risk factors for ovarian carcinoma evaluated with 31 items for a family history of ovarian and other types of carcinoma, past history, preferences, and social background. Obesity and a family history of breast carcinoma and endometrial carcinoma have been proven to be independent risk factors, and infertility, age . 50 years, and a family history of pancreatic carcinoma were important risk factors (Table 5). It may be possible to reduce the subjects to 45% if the 6 factors are used for questioning during screening. It also may be possible to make screening for ovarian carcinoma as cost-effective as screening for uterine cervical carcinoma because the 24 patients with ovarian carcinoma in the current study were found to have at least 1 of these factors. Attention is given to familial factors in Europe and the U.S.,15–17 but a family history of ovarian carcinoma was not considered to be a risk factor in the current study. The number of deliveries18 and the use of oral contraceptives,19,20 which reportedly reduce the risk of ovarian carcinoma, showed no significant correlation with ovarian carcinoma risk. Obesity was found to be correlated significantly with the risk of ovarian carcinoma, but it may be necessary to determine the risk factors based on the differences in nationality or life-style because of an epidemiologic report on similar prevalence rates in Japanese-American and white women.21

Pavlik et al.22 calculated the cost of TVS screening for ovarian carcinoma based on their experience. The cost, which initially was U.S.$600 or more per woman, decreased to U.S.$25. Given a diagnostic rate of 1/1000 in TVS, the cost for screening is U.S.$25,000 and the cost for treatment of Stage I carcinoma is U.S.$10,000, with other costs running to approximately U.S.$45,000, for a total of U.S.$80,500. The cost of TVS screening was U.S.$170,000 less than the estimated total costs required for a patient with advanced disease (from diagnosis to death) of U.S.$250,000. These estimates may not be applied easily to the situation in Japan, where the prevalence of ovarian carcinoma is considerably lower than that in Europe and the U.S. However, in light of the estimated increase in the incidence rate of ovarian carcinoma, it may be necessary to establish a more efficient diagnostic system for early ovarian carcinoma.
Mackey and Creasman evaluated tumor marker measurement, transabdominal and transvaginal ultrasonography, and transvaginal color flow imaging as a form of screening for ovarian carcinoma and mentioned the need for comprehensive, long term studies comparing mortality between participants and nonparticipants prior to determining which method is effective. The National Institutes of Health Consensus Conference reported that screening using CA 125 or TVS does not appear to contribute to a reduction in mortality from ovarian carcinoma. These conclusions may be natural because there may have been an insufficient number of cases, a high false-negative rate in tumor marker measurement for early ovarian carcinoma in particular, and inefficiency in their ultrasonographic methods, which took a great deal of time. We believe that our screening method using TVS with simple criteria and a reduction in time may be a viable method for fulfilling the purpose of the early detection of ovarian carcinoma at a high rate.

REFERENCES
Ovarian cancer is the fifth most common cancer in women and the most common cause of gynecologic cancer deaths. In 2008, about 22,000 women will be diagnosed with ovarian cancer, with approximately 15,500 women dying from the disease. Approximately one in 70 women will develop ovarian cancer in her lifetime.

While the most common recognized risk factor associated with the disease is advancing age, other factors contributing to an increased risk of the disease include infertility, endometriosis (a condition in which tissue from the lining of the uterus grows outside of the uterus), and post-menopausal hormone replacement therapy. Additionally, some studies have suggested — but other studies have not confirmed — that use of assisted reproductive technologies such as in vitro fertilization may increase a woman’s risk of developing ovarian cancer. It is important to note, however, that these age-independent risk factors do not significantly increase a woman’s chances of developing ovarian cancer, elevating a woman’s risk level no more than two to three times higher than that of the general population.

Recommendations for ovarian cancer screening traditionally have been organized into one of two sets of guidelines — one for women at average risk and the other for women at increased risk. Now, with the identification of gene mutations that can increase a woman’s chances of developing ovarian cancer, the set of guidelines for women at an increased risk has been subdivided into two groups, with recommendations for women with a clear inherited risk of developing ovarian cancer due to an identified genetic mutation differing from those for women with a family history of the disease. This concept of variable risk has been incorporated into Memorial Sloan Kettering’s current recommendations for ovarian cancer screening.

Ovarian Cancer Risk Types

Women with a risk level near that of the general population (relative risk less than three times the relative risk of the general population)

This category includes women with any of the following:

- A history of breast cancer diagnosed at age 41 or older and a) no family history of breast or ovarian cancer or b) no Ashkenazi Jewish heritage (individuals of Eastern European Jewish descent from Eastern Europe).
- A history of infertility and/or use of assisted reproductive therapies, such as in vitro fertilization (IVF).
- A history of endometriosis (a condition in which tissue from the lining of the uterus grows outside of the uterus).
- A history of hormone replacement use for the management of symptoms related to menopause.

Women with increased risk* (relative risk three to six times greater
than that of the general population

This category includes woman with any of the following:

- A first degree relative (mother, sister, or daughter) with ovarian cancer.
- A personal history of breast cancer prior to age 40.
- A personal history of breast cancer diagnosed prior to age 50, and one or more close relatives diagnosed with breast or ovarian cancer at any age.
- Two or more close relatives diagnosed with breast cancer prior to age 50 or with ovarian cancer diagnosed at any age.
- Ashkenazi Jewish heritage and a personal history of breast cancer prior to age 50.
- Ashkenazi Jewish heritage and a first- or second-degree relative diagnosed with breast cancer prior to age 50 or with ovarian cancer at any age.

* These estimates are obtained from studies in which genetic testing information was not available. For individuals who meet the family history criteria but have tested negative for a genetic mutation known to increase susceptibility to the disease, the risk of developing ovarian cancer may be substantially lower. These women should consult a medical professional for screening recommendations.

Women with inherited risk due to known genetic mutations (relative risk greater than six times that of the general population)

This category includes woman with any of the following:

- Presence of a BRCA1 or BRCA2 mutation. BRCA1 and BRCA2 are genes involved in cell growth, division, and repair of damage to DNA that occurs naturally during one’s lifetime. An altered, or mutated, BRCA1 or BRCA2 gene increases the likelihood that cancer will develop. The most common types of cancers associated with BRCA alterations are breast and ovarian cancer.
- Presence of a mismatch repair gene mutation associated with a hereditary cancer syndrome known as Hereditary Non-Polyposis Colon Cancer (HNPCC)/Lynch syndrome.

Mutations in the genes known to increase susceptibility to ovarian cancer likely account for a large proportion of the incremental risk among women with a family history of ovarian or breast cancer diagnosed before the age of 50. Preliminary evidence has suggested that women with a strong family history of breast cancer but no demonstrable mutation in BRCA1 or BRCA2 may not be at significantly increased risk of ovarian cancer. For this reason and due to the limitations of currently available ovarian cancer screening tests, which are described below, women in the increased risk category should consider genetic counseling and testing prior to initiating ovarian cancer screening or other ovarian cancer risk-reduction strategies.

Ovarian Cancer Screening Tests

A number of tests have been evaluated as potential methods of screening for ovarian cancer. Screening tests with the greatest amount of clinical test data supporting their use include transvaginal ultrasound and the blood test for the serum marker CA-125. (Serum markers are substances in the blood that can be detected in blood tests.) Less information is available regarding a number of other serum markers, used alone or in combination. A newer test based on proteomics, a method which involves the evaluation of patterns of dozens to hundreds of low molecular weight proteins simultaneously, has also been recently proposed.
CA-125

CA-125 is a protein produced by more than 90 percent of advanced epithelial ovarian cancers. (Epithelial ovarian cancer is the most common form of the disease.) As a result, the CA-125 protein has become the most evaluated serum marker for ovarian cancer screening. In the largest study to date, 22,000 post-menopausal women at average risk of ovarian cancer were randomly chosen to receive either annual CA-125 tests or their usual gynecologic care. In this study, women with ovarian cancer detected by the CA-125 tests had improved survival compared to women diagnosed with ovarian cancer who were assigned to their usual care. While these results were promising, there was no difference between the two groups in the number of deaths due to ovarian cancer. Additionally, although 8,732 women were screened, only six ovarian cancers were detected, with three of these being at an advanced stage.

Other studies have suggested that CA-125 also appears to be elevated in two to three percent of normal post-menopausal women. Given this fact and the relatively low annual incidence of ovarian cancer, screening using the CA-125 test has not been effective enough to warrant its widespread use. For ovarian cancer to be detected in one additional woman using CA-125 as the primary screening method, another 100 to 150 women would have to receive evaluation and approximately 30 diagnostic operations be performed.

To improve the utility of CA-125 measurements for ovarian cancer screening, a method has been proposed that focuses on the change in CA-125 concentration in the bloodstream over time, as opposed to relying on the absolute value. This approach is being used in an ongoing study in Great Britain, in which 200,000 women will be randomly assigned to receive screening with CA-125, screening with transvaginal ultrasound, or their usual care. Results from this study are expected in 2012.

Transvaginal Ultrasound

A number of imaging methods have been evaluated for possible use in ovarian cancer screening. Transvaginal ultrasound has consistently proven to be the most promising imaging method for routine screening of ovarian cancer.

In the largest study to date evaluating ultrasound as a screening method for ovarian cancer, 14,469 women, most of whom were at average risk for ovarian cancer, were monitored using annual transvaginal ultrasounds. Promisingly, 11 of 17 cancers detected by transvaginal ultrasound screening were diagnosed at the earliest stage of the disease, known as stage I. Critics, however, have pointed out than only two of the 11 stage I cancers detected by transvaginal ultrasound were high grade (meaning that the cancer cells have an aggressive growth rate), compared to all six of the advanced stage cancers.

Serum CA-125 in Combination with Transvaginal Ultrasound

Several studies have evaluated the combined use of transvaginal ultrasound and CA-125. These studies have suggested that the combination of these tests result in a higher sensitivity for ovarian cancer detection, but at the cost of an increased rate of false positive results. In an ongoing prostate, lung, colorectal, and ovarian cancer screening trial, 28,816 women were randomly chosen to receive annual transvaginal ultrasound and CA-125 testing. An additional 39,000 women were randomly assigned to a control group in which they received only their usual gynecologic care. The positive predictive values for an abnormal test were one percent for transvaginal ultrasound and 3.7 percent for CA-125. When both were abnormal, this value increased to 23.5 percent. Final results, including impact of screening on ovarian cancer mortality, are expected in 2015.
Our Ovarian Cancer Screening Guidelines

Women with a risk near that of the general population (relative risk less than three times greater than that of the general public)

- Ovarian cancer screening is not recommended. An annual gynecologic examination with pelvic examination is recommended for preventive healthcare.

Women with increased risk (relative risk of three to six times greater than that of the general public)

- There is no clear evidence to suggest that ovarian cancer screening with currently available methods will result in a decrease in the number of deaths from ovarian cancer. If, after careful consideration of risks and benefits, ovarian cancer screening with serum markers such as CA-125 and/or transvaginal ultrasound is to be pursued, it is recommended that such screening be done within the framework of research studies to evaluate the efficacy of this approach.

Genetic counseling may also be helpful for women in this group to better clarify the risk of ovarian and related cancers.

Women with inherited risk (relative risk more than six times greater than that of the general public)

- While it is not clear that ovarian cancer screening will result in a decrease in the number of deaths in women at inherited risk, those who have mutations in ovarian cancer susceptibility genes should undergo ovarian cancer screening using a combination of transvaginal ultrasound and CA-125 testing. For women with mutations in BRCA1 or the mismatch repair genes, MLH1, MSH2, and MSH6, this screening should generally begin between ages 30 and 35. For women with mutations in BRCA2, ovarian cancer screening should be initiated between ages 35 and 40.

Given the limitations of ovarian cancer screening, including the substantial risks of both false positive and false negative results, risk-reducing salpingo-oophorectomy (a surgical procedure that removes a woman’s ovaries and fallopian tubes) should be considered upon conclusion of childbearing by women with documented inherited predispositions.

Further information regarding screening and risk-reduction recommendations for women who are members of known hereditary cancer families are summarized in our Hereditary Cancer & Genetics section.

References


8. [PubMed Abstract]


10. [PubMed Abstract]

11. [PubMed Abstract]


15. [PubMed Abstract]


17. [PubMed Abstract]

18. [PubMed Abstract]


20. [PubMed Abstract]


22. [PubMed Abstract]

23. [PubMed Abstract]


25. [PubMed Abstract]


29. [PubMed Abstract]


Study: Screening shows promise in early ovarian cancer detection

Preliminary results from a United Kingdom study found that two screening strategies – the CA-125 blood test and a painless transvaginal ultrasound – are effective at finding ovarian cancer early, when it is more easily treated.

Most women are diagnosed with Stage III or IV ovarian cancer, resulting in a high fatality rate.

Overall, the study found that 48.3 percent of the cancers detected by transvaginal ultrasound alone or with a combination of ultrasound and blood test were at an early stage (Stage I or Stage II). About 90 percent of women with Stage I ovarian cancer at the time of detection are cured with conventional treatment.

Traditionally, however, most women are diagnosed with Stage III or IV ovarian cancer, resulting in a high fatality rate. The five-year survival rate for women diagnosed with Stage III or IV cancer is 27 percent and 16 percent respectively, the researchers reported.

How the study was conducted

The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) was launched in 2001. The results, reported in the April issue of *Lancet Oncology*, represent screenings of about 100,000 women through 2005. Researchers will follow up through 2014 before the final results will be reported. Ultimately, the study is designed to answer whether screening for ovarian cancer is effective in saving women’s lives.

The initial results come from 202,638 postmenopausal women ages 50 to 74 (average age of nearly 61) recruited from 27 centers in England, Wales and Northern Ireland. In this randomized, controlled trial, half of the women were not screened; one-fourth had an annual screening with the blood test for CA-125, which checks for tumor markers indicative of ovarian cancer, followed by transvaginal ultrasound if necessary; and one-fourth had an annual screening with transvaginal ultrasound alone.

Women who had screenings with abnormal findings had repeated screenings and were referred for further evaluation and treatment, including surgery, if necessary.

Study findings

Researchers reported that either screening method found most of the diagnosed ovarian cancer cases: 34 of 38 cases (90 percent) were found with the combined screenings; 24 of 32 cases (75 percent) with the transvaginal ultrasound alone. Twenty-eight of the 58 cancers (48.3 percent) found were early – Stage I or II.

Repeat testing was needed more often in those women who underwent ultrasound screening alone (12 percent versus 9.1 percent with the combined screening). Also, those in the ultrasound-
screening alone group were more apt to have surgery, which researchers said was due to the higher prevalence of benign lesions in postmenopausal women. Based on these preliminary findings, the study authors said that both transvaginal ultrasound and the CA-125 blood test “remain at the core of all new screening and diagnostic strategies being proposed for ovarian cancer” with both strategies demonstrating “encouraging performance characteristics.”

**Study: Screening shows promise in early ovarian cancer detection**

**Study limitations**

The authors note a limitation of the study was not using a morphological (form and structure) index that may improve the ability of doctors to tell the difference between benign (noncancerous) and cancer tumors on ultrasound scans. They also noted that they did not collect data on cancers in the control group, and a study selection process may have resulted in a high number of healthy participants.

---

Ovarian screening combo may increase survival rates

This is a good study. It confirms that screening can detect ovarian cancer at an earlier stage than it’s normally detected without screening. It also establishes the fact that the combination of the blood test for ovarian cancer – CA-125 – with ultrasound is probably more effective than ultrasound alone.

Of women whose ovarian cancer was detected by screening, 82 percent had Stage I or II disease compared to 30 percent of women in the unscreened population.

But this study doesn’t answer the question of what is the optimal screening algorithm. I don’t think anyone believes that either CA-125 alone or ultrasound alone is as effective as both of them together in finding ovarian cancer early. The question remains, which is better first? Is it better to do it as we are doing it here at the University of Kentucky, with the transvaginal ultrasound first and then use other methods to increase the positive predictive value of the ultrasound? Or is it better to use CA-125 first? We are trying to develop an ideal algorithm for screening in order to detect ovarian cancer earlier.
Local study provides insight

We started our ovarian cancer screening study in 1987 and published our first results in 1991. Our findings demonstrate that annual screening with ultrasound improves early detection and saves women’s lives. We are accruing about 10,000 patients a year throughout Kentucky into our study and have now screened 35,000 women for an average of six years. Our study is the largest institutional ovarian screening trial in the United States.

“The ultimate cure rate for a woman with advanced ovarian cancer is only about 10 percent. So clearly, something needs to be done to increase early detection.”

In our study, if the ultrasound is abnormal, we perform a repeat ultrasound in four weeks. If the repeat ultrasound is abnormal, we perform a CA-125 blood test and morphology indexing. Although sonography (another word for ultrasound) can reliably detect even small ovarian tumors, it is not completely accurate in differentiating a benign ovarian tumor from ovarian cancer. We use morphology (form and structure) indexing to identify certain patterns that are associated with benign or noncancerous tumors. If the patient’s CA-125 is normal and the morphology index indicates a benign tumor, she may not need to have surgery and can be followed periodically with repeat ultrasound.

Both our study and the trial from the United Kingdom detected ovarian cancer at a significantly earlier stage than when women did not have screening. The University of Kentucky Ovarian Cancer Screening Program is an ongoing trial; we published results from this trial in 2007 in the journal Cancer. What we showed was that 82 percent of women whose ovarian cancer was detected by screening had Stage I or II disease compared to 30 percent of women in the unscreened population.

Without screening, about 70 percent of women present with Stage III or IV disease. This is important to note because only 30 percent of women with advanced ovarian cancer will be alive in five years after treatment and two-thirds of them will still have disease that cannot be cured. Therefore, the ultimate cure rate for a woman with advanced ovarian cancer is only about 10 percent. So clearly, something needs to be done to increase early detection.

Limitations of the pelvic exam

We also have done studies here at the University of Kentucky that show routine pelvic examination is not effective in detecting small ovarian tumors. Therefore, you may have a pelvic examination that is reported as normal, but still have a small undetectable ovarian abnormality. Pelvic examinations just do not reliably pick up early ovarian cancer, particularly in women who are overweight or who have a large uterus.
Signs of ovarian cancer

As a gynecologic oncologist, it is frustrating and tragic to see women presenting with advanced ovarian cancer. Recent research has indicated that ovarian cancer may produce specific symptoms. These symptoms include bloating, early fullness after eating and pelvic pain. If a postmenopausal woman suddenly develops these symptoms, she should contact a physician for further evaluation. We hope that as a result of the work we and others have done, every woman over the age of 55 will one day be able to get an ultrasound at the time of her annual pelvic examination.

Dr. van Nagell is director of gynecologic oncology at UK Markey Cancer Center and professor of obstetrics and gynecology at the UK College of Medicine.

Screening for ovarian cancer
The Ovarian Cancer Screening Program is one of the Markey Cancer Center’s clinical research trials aimed at improving the health conditions of women across the Commonwealth.

Postmenopausal women over the age of 50 without symptoms or women over the age of 25 with a documented history of ovarian cancer are eligible to participate. Screening involves transvaginal ultrasound imaging of the ovaries. The test, which takes 5 to 10 minutes, is painless.

Directed by Dr. John R. van Nagell, this program provides free ovarian screenings in Lexington, Elizabethtown, Somerset, Prestonsburg, Maysville and Paducah. For more information, call toll free 1-800-766-8279 or 859-323-4687.
Editorial

Ultrasound and Doppler in Gynecological Cancers

The scope of ultrasound in gynecology is vast. It is virtually an extension of the clinical examination in most gynecological conditions due to its accessibility, relatively low cost, and risk, and high patient acceptance. Its applications in women with cancer are expanding rapidly. Ultrasound is used for screening (endometrium, ovary), diagnosis (evaluation of the adnexal mass) and follow-up of therapy for detection of recurrences. Transabdominal and transvaginal ultrasound are both useful in evaluation of women with gynecological cancer. The transabdominal route is mandatory for fully assessing large masses extending outside the pelvis and for evaluating the upper abdomen. The transvaginal route is preferable for most other situations where smaller masses and the pelvic structures are to be visualized. Color Doppler is an additional modality which can be used for differentiating benign and malignant disease. Malignancy is characterized by a rapid cell proliferation and tissue generation. This is accompanied by the formation of new blood vessels which support this growth. The neangiogenesis is characterized by a lack of muscular media, chaotic arrangement, arteriovenous shunts and low resistance flows. These characteristics can be assessed by Doppler and could be considered as corroborative evidence of malignancy.

Despite the advances in surgery and chemotherapy, the 5-year survival rate of women with epithelial ovarian cancers has not changed much over the years. This is because most ovarian cancers are detected in late stages of the disease due to a lack of specific symptoms. The application of ultrasound as a screening tool for ovarian malignancy is based on its ability to detect tumors which are asymptomatic and not clinically palpable. Smaller cancers are likely to be less widespread and offer the best prospects of improving therapeutic results. In the early days, ultrasound was used alone and was not considered a useful tool for screening. Early studies were hampered by poor sensitivity and specificity. 67 laparotomies were required to detect one early stage ovarian cancer. There have been numerous technical and methodological refinements to sonography over the last decade. Characterization of ovarian and adnexal masses has been achieved with much greater clarity. The ultrasound features of a malignant growth have been described as bilateral, large size (>5 cm), multiple locules, papillary excrescences or solid areas, presence of ascites or metastasis. The addition of Doppler and serum marker such as CA-125 has been used as a multimodality screening strategy. A risk of malignancy index (RMI) is a useful tool for the preoperative assessment of adnexal masses. A recently concluded prospective study evaluated 202 638 postmenopausal women randomized to no screening, ultrasound only screening and multimodality screening. The sensitivity (89.5%) and specificity (99.8%) of the multimodality approach were superior to the other groups in detecting early ovarian cancer. It was estimated that only 3 laparotomies would be needed to detect one early stage ovarian cancer. This represents a significant improvement from earlier studies and is an indicator of the potential of a multimodality screening approach for ovarian cancer in postmenopausal women. Color

![Image]

Figure 1. Color Doppler blood flow showing a low resistance index (RI = 0.27) in a malignant ovarian tumor.
Doppler has been studied in its role in detecting vascular flow patterns and characterizing the resistance to blood flow in ovarian tumors. Malignant growths are characterized by neovascularization and blood vessels with a poorly developed muscularis. The blood flow in these vessels is marked by low impedance and correspondingly, the resistance index is low (RI < 0.3) as in Figure 1. In contrast, benign ovarian tumors and normal ovarian blood flow is characterized by a high RI (Figure 2).  

Screening for endometrial cancer is currently based on a risk factor approach. Postmenopausal bleeding is the prime indicator for the risk of endometrial cancer and transvaginal ultrasound is the first step in the triage for these women. Endometrial thickness has been extensively studied as a predictor of endometrial malignancy. Meta-analysis have shown that when the endometrial thickness is less than 5 mm, the risk of endometrial malignancy is about 1 in 100. In such cases, endometrial sampling and histopathology can be avoided. The significance of thick endometrium in non-bleeding postmenopausal women has not been validated and is not an automatic criteria for endometrial sampling. Other ultrasound markers of malignancy are the disturbance of the interface between the endometrium and myometrium and presence of irregular, vascular mass lesions inside endometrial cavity. Color Doppler is useful as an adjunct in diagnosing endometrial cancer. The subendometrial blood flow and the blood flow in thickened and polypoidal endometrium shows low resistance patterns in endometrial malignancy and the RI is usually less than 0.3. Saline infusion sonography is useful in detecting polyps and intracavitary masses. Preoperative assessment with ultrasound results matches the result of a CT or MRI assessment.

Conventionally, ultrasound and Doppler have no role in diagnosis of cervical cancer. Ultrasound has limited value in predicting parametrial and nodal spread of cervical cancer. It does not compare favourably to other imaging techniques such as CT or MRI. New ultrasound modalities such as 3D ultrasound and volume analysis are being studied as prognostic markers and are under evaluation.

The battle of malignancy is fought at the basement membrane. An early diagnosis is the key to improving survival. Ultrasound and Doppler are being widely studied for their potential to screen for ovarian and endometrial cancer to increase early detection and should be considered as a part of the annual gynecological visit. The ability to guide clinical and preoperative decision-making is an additional benefit. Its application in other malignant conditions is finding increasing acceptance and clinical application.

References

Three-dimensional (3D) reconstruction of ultrasound images was first demonstrated nearly 15 years ago but only now is becoming a clinical reality. In the meantime, methods for 3D reconstruction of computed tomography (CT) and magnetic resonance imaging (MRI) have achieved an advanced state of development, and 3D imaging with these modalities has been applied widely in clinical practice. Three-dimensional applications in ultrasound have lagged behind CT and MRI, because ultrasound data is much more difficult to render in 3D, for a variety of technical reasons, than either CT or MRI data. Only in the past few years has the computing power of ultrasound equipment reached a level adequate enough for the complex signal processing tasks needed to render ultrasound data in three dimensions. Within the past years several new ultrasound techniques have appeared. Three-dimensional ultrasound scanning, in which there has been great interest, is one of them [1]. Especially within obstetrics and gynecology several papers on that topic describe promising results. Gynecologic diagnostics relying on morphologic signs and accurate distance and volume measurements is one of the areas believed to benefit from 3D ultrasound; however, until now only few prospective works have been published, most of them counted as preliminary. One of the main reasons might be the huge technologic challenge. It is proposed that technologic progress over the next few years will allow feasible real-time 3D scanning. Gynecologic ultrasound scanning will thereby undoubtedly take another giant leap forward.

Why do we need 3D ultrasound in gynecology? Great strides have been made in gynecology secondary to the development of high-performance transvaginal ultrasound (TVS) instruments; however, even this advanced technology can provide only two-dimensional (2D) views of three-dimensional (3D) structures. Although an experienced examiner can easily piece together sequential 2D planes for creating a mental 3D image, individual sectional planes cannot be achieved in a 2D image because of various difficulties. Presently, 3D TVS can portray not only individual image planes, it can also store complex tissue volumes which can be digitally manipulated to display a multiplanar view, allowing a systematic tomographic survey of any particular field of interest. The same technology can also display surface rendering and transparency views to provide a more realistic 3D portrayal of various structures and anomalies.

Technique

Since the end of the 1980s, 3D ultrasound has become a major field of research in gynecology. The technique of acquiring 3D data involves making a set of consecutive 2D ultrasound slices by moving the transducer and continuously storing the images. These ultrasound data must be converted into a regular cubic representation before presentation in different 3D visualization modes. The creation of new ultrasound sections from the 3D block, and also the surface shading of a structure of interest, promise improvement in the diagnosis of congenital anomalies and pelvic masses. In addition, the possibility of volume calculation by 3D ultrasound has to be considered as a clear innovation. At present, almost all of the diagnoses illustrated by 3D ultrasound can be made by 2D ultrasound, and this will continue to be so in the foreseeable future. Recently, computer-assisted treatment of sonographic images has permitted 3D reconstruction in gynecology. This is achieved by scanning a given volume containing the organ of interest. Two practical options exist. Some ultrasound probes are equipped with an automatic scanning device while others use manual scanning, electronically normalized or not. Both approaches make use of an electronic matrix, i.e., a pile of 2D sonographic images. Secondary cuts are possible through the electronic matrix, including plans not normally accessible to ultrasound scanning because of anatomical limitations. One of the secondary cuts most clinically useful is the frontal plane of the uterus. This enables one to visualize the organ lying flat as it is commonly drawn on medical sketches. Studying the frontal plane of the uterus acquired electronically from a 3D matrix improves the visualization of possible interactions between structures such as uterine fibroids and the endometrium. The
frontal plane of the uterus also offers marked improvements for studying uterine malformations.

Three-dimensional ultrasound offers several options extending conventional 2D scanning. Various imaging modes are available. Three perpendicular planes displayed simultaneously can be rotated and translated in order to obtain accurate sections and suitable views needed for diagnosis and geometric measurements. Three-dimensional ultrasound tomography combines the advantages of ultrasound, e.g., safety, simplicity of application and inexpensiveness, with the advantages of sequentially depictable sections in numerous rotatable and translatable sections. Surface rendering gives detailed plastic images if there are surrounding layers of different echogenicity allowing for the definition of a certain threshold. Transparent modes provide an imaging of structures with a higher echogenicity in the interior of the object. A combination of the two modes sequentially definable by the sonographer allows for the optimal viewing of structures. These imaging modes are innovative features that have to be evaluated for clinical applicability and usefulness (Fig. 38.1). Digital documentation of whole volumes enables full evaluation without loss of information at a later point. The 3D technology provides an enormous number of technical options that have to be evaluated for their diagnostic significance and limitations in obstetrics and gynecology.

**3D Doppler Measurements**

Doppler methods are routinely used to study the vascular system. Flow and tissue motion information can be obtained by frequency and time-domain processing. Instruments range in complexity from simple continuous-wave devices without imaging capability through advanced real-time 2D color-flow scanners and intra-vascular devices. A 3D display is now available. Contrast agents can be used to increase the detectability of blood flow signals. The properties of the tissue impose an envelope on achievable ultrasonic imaging. Doppler studies can provide information about flow velocity profile, vessel compliance, wall shear rate, pressure gradient, perfusion, tumor blood flow, and the presence of emboli. These capabilities can be integrated into a holistic picture of ultrasonic vascular studies [2, 3].

Three-dimensional Doppler ultrasound has the potential to study pelvic blood flow and process of neovascularization. The 3D Doppler superimposed to 3D gray scale can detect early vasculogenesis within the uterine or adnexal mass. Traditionally, we defined blood flow information as (a) quantitative, i.e., volume flow measurements (cc/min), and (b) semiquantitative, i.e., pulsatile Doppler waveform analysis (RI, PI, S/D index).

Three-dimensional power Doppler introduces a new way to look at blood flow detection and analysis. Using the computer-generated VOCAL imaging program (virtual organ computer-aided analysis), different patterns of blood flow can be described:

1. Vascularization index (VI)
2. Flow index (FI)
3. Vascularization flow index (VFI)

Vascularization index gives information (in percentage) about the amount of color values (vessels) in the observed organ or area (e.g., uterus, ovary, or mass). Flow index is a dimensionless index (0–100) with information about intensity of blood flow. It is calculated as a ratio of weighted color values (amplitudes) to the number of color values. Vascularization flow index (VFI) is combined information of vascularization and mean blood flow intensity. It is also a dimensionless index (1–100) that is calculated by dividing weighted color values (amplitudes) by the total voxels minus background voxels. Three-dimensional Doppler was used to acquire volumes (Fig. 38.2). VOCAL was then used to delineate the 3D areas of interest (Fig. 38.3) and the “histogram facility” employed to generate three indices of vascularity: the VI; the FI; and the VFI (Fig. 38.4). The ultrasonographer should be aware that 3D Doppler is prone to the same artifacts and pitfalls as 2D Doppler. This information should be taken into account when any assessment of pelvic or tumor blood flow is made.

**3D Doppler in Human Reproduction**

Three-dimensional Doppler ultrasound is a new modality finding its way into clinical practice. We discuss recent publications related to 3D Doppler applications in human reproduction, gynecologic oncolog-
ology, and in the field of benign gynecology, Pan et al. aimed to test the hypothesis that the decreased ovarian sensitivity to gonadotropins observed in women embarking on an in vitro fertilization (IVF) treatment may be due to changes in ovarian stromal blood flow [4]. They used 3D power Doppler ultrasonographic indexes to quantify ovarian stromal blood flow and vascularization in poor responders. Forty patients undergoing an IVF cycle were collected and divided into two groups, a poor responder group (n = 17; estradiol <600 pg/mL or ≤3 oocytes retrieved) and normal responder group (n = 23), based on their response to a standard down-regulation protocol for controlled ovarian stimulation. During ovarian stimulation, on the day of administration of human chorionic gonadotropin (HCG), patients underwent hormonal (serum E2), ultrasonographic (follicular number and diameter), and 3D power Doppler (ovarian stromal blood flow) evaluation. Compared with poor responders, the serum estradiol levels on the day of administration of HCG, the number of follicles >14 mm, the number of oocytes retrieved, the number of embryos transferred, and the pregnancy rate were significantly higher in normal responders. The vascularization index, flow index, and vascularization flow index were significantly lower in the poor responders compared with the women with a normal response. They concluded that the 3D power Doppler indexes of ovarian stromal blood flow in poor responders was significantly lower than those of normal responders. This may help to explain the poor response during HCG administration in controlled ovarian stimulation.

The British group used 3D power Doppler to examine the periodic changes in endometrial and sub-endometrial vascularity during the normal menstrual cycle in 27 women without obvious menstrual dysfunction or subfertility [5]. Doppler exam was performed on alternate days from day 3 of the cycle until ovulation and then every 4 days until menses. Virtual organ computer-aided analysis and shell imaging were used to define and to quantify the power Doppler signal within the endometrial and sub-endometrial regions producing indices of their relative vascularity. Both the endometrial and sub-endometrial VI and VFI increased during the proliferative phase, peaking approximately 3 days prior to ovulation before decreasing to a nadir 5 days post-ovulation; thereafter, both vascular indices gradually increased.
Fig. 38.3. Virtual organ computer-aided analysis was then used to delineate the 3D areas of interest.

Fig. 38.4. The "histogram facility" was employed to generate three indices of vascularity: the vascular index, the flow index, and the vascularization flow index.
during the transition from early to mid-secretory phase. The FI showed a similar pattern but with a longer nadir post-ovulation. Smoking was associated with a significantly lower VI and VFI. The FI was significantly lower in women aged ≥31 years and significantly higher in parous patients. The authors concluded that endometrial vascularity, as assessed by 3D Doppler, varies significantly during the menstrual cycle and is characterized by a pre-ovulatory peak and post-ovulatory nadir during the peri-implantation window.

Three-dimensional power Doppler has been largely used for the subjective assessment of vascular patterns, but semiquantification of the power Doppler signal is now possible. Kaine-Fenning et al. addressed the intraobserver and interobserver error of the semiquantification of pelvic blood flow using 3D Doppler, VOCAL, and shell imaging [6]. The 3D Doppler was used to acquire 20 ovarian and 20 endometrial volumes from 40 different patients at various stages of in vitro fertilization treatment. The VOCAL was then used to delineate the 3D areas of interest and the “histogram facility” employed to generate three indices of vascularity: the VI; the FI; and the VFI. Intraobserver and interobserver reliability was assessed by two-way, mixed, intraclass correlation coefficients (ICCs) and general linear modeling was used to examine for differences in the mean values between each observer. The intraobserver reliability for both observers was extremely high and there were no differences in reliability between the observers for measurements of both volume and vascularity within the ovary or endometrium and its shells. With the exception of the outside sub-endometrial shell volumes, there were no significant differences between the two observers in the mean values obtained for either endometrial or ovarian volume and vascularity measurements. The interobserver reliability of measurements was equally high throughout with all measurements obtaining a mean ICC of above 0.985. They concluded that 3D Doppler and shell imaging offer a reliable, practical, and non-invasive method for the assessment of ovarian, endometrial, and sub-endometrial blood flow. Future work should concentrate upon confirming the reliability of data acquisition and the validity of the technique before its predictive value can be truly tested in prospective clinical studies.

Vlašavljević et al. wanted to study whether they might predict the outcome of unstimulated in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) cycles with quantitative indices of perifollicular blood flow assessed with 3D reconstruction of power Doppler images [7]. This prospective study included an analysis of 52 unstimulated cycles. Color and power Doppler ultrasound examinations of a single dominant preovulatory follicle were performed on the day of oocyte pick-up. With 3D reconstruction and processing, quantitative indices were obtained, i.e., the percentage of volume showing a flow signal (VFS) inside a 5-mm capsule of perifollicular tissue and the percentage of VFS of each of the three largest vessels in this capsule. These indices as well as pulsed Doppler indices were compared between the groups of cycles with different outcomes using a one-way analysis of variance test. In nine cycles no oocyte was retrieved (group A), in seven cycles no fertilization occurred (group B), and in 30 cycles no implantation occurred (group C). Six cycles resulted in pregnancy (group D). There were no statistically significant differences in pulsed and power Doppler indices between these groups; however, the percentage of VFS in the capsule was higher than average in cycles with implantation and the percentage of VFS in the main vessel exhibited lower than average values in cycles with implantation, but only reached borderline statistical significance. It can be hypothesized that the follicles containing oocytes able to produce a pregnancy have a distinctive and more uniform perifollicular vascular network.

Other authors also looked at 3D Doppler of the ovary and relationship with hormonal status in IVF patients. Wu et al. investigated, in a retrospective study, whether the quantification of ovarian stromal blood flow and/or leptin concentration are predictive of IVF outcomes in women after laparoscopic ovarian cystectomy for large endometriomas [8]. Twenty-two women undergoing IVF after laparoscopic surgery for ovarian endometriomas (>6 cm) comprised the study group. Twenty-six women with tubal factor infertility constituted the control group. Ovarian stromal blood flow was evaluated by 3D power Doppler ultrasound imaging using VOCAL. Serum and follicular fluid (FF) leptin concentrations were quantified using an enzyme-linked immunosorbent assay kit. There were significantly decreased ovarian stromal blood flow parameters (including VI, FI, and VFI) in the endometriosis group without an evident difference in total ovarian volume on the day of human chorionic gonadotropin. The value of FF leptin demonstrated a negative correlation with ovarian stromal FI in the control group, but there was a loss of this effect in the endometriosis group. It appeared that the quantification of ovarian stromal blood flow by 3D power Doppler ultrasound in women with endometriosis may provide an important prognostic indicator in those undergoing IVF.

Kupesic and Kurjak designed the study to evaluate whether ovarian antral follicle number, ovarian volume, stromal area, and ovarian stromal blood flow are predictive of ovarian response and IVF outcome [9]. A total of 56 women with normal basal serum FSH concentrations who had no history of ovarian surgery and no ovarian and/or uterine pathology
were non-smokers and undergoing their first IVF cycle using a standard long GnRH-agonist protocol were examined. Total ovarian antral follicle number, total ovarian volume, total stromal area, and mean PI of the ovarian stromal blood flow were determined by 3D and power Doppler ultrasound after pituitary suppression. Pretreatment 3D ultrasound ovarian measurements were compared with subsequent ovulation induction parameters [peak estradiol (E2) on HCG administration day and number of oocytes] and cycle outcome (fertilization and pregnancy rates). The total antral follicle number achieved the best predictive value for favorable IVF outcome, followed by ovarian stromal PI, peak E2 on HCG administration day, total ovarian volume, total ovarian stromal area, and age. Using these six parameters, they were able to predict a favorable IVF outcome in 50% (11 of 22) of patients and poor outcome in 85% (29 of 34) of patients. Three-dimensional ultrasound facilitates determination of the antral follicle number, ovarian volume calculation, evaluation of the ovarian stroma, and analysis of the intensity of ovarian stromal blood flow in a short time without increasing the patients discomfort.

The study done by Schill et al. was designed to investigate the role of 3D power Doppler sonography of the sub-endometrial area on the first day of ovarian stimulation in predicting the outcome of an IVF program [10]. Among the 75 cycles analyzed, the overall pregnancy rate was 20% (15 of 75) per cycle and 23.8% (15 of 63) per embryo transfer. Intraobserver variability of the color histogram was checked in 14 patients with the results demonstrating a high level of agreement. Neither endometrial measurements nor uterine blood flow were correlated with the pregnancy rate. In contrast, all 3D indices were significantly lower in conception compared with non-conception cycles. Logistic regression analysis found the sub-endometrial flow index to be the strongest predictive factor of IVF success among the tested sonographic parameters. In conclusion, quantitative assessment of spiral artery blood flow may be of predictive value for implantation in IVF cycles even before ovarian stimulation therapy is started.

3D Doppler in Gynecologic Oncology

The differentiation of benign from malignant pelvic mass is still a considerable clinical challenge using traditional 2D real-time and Doppler ultrasound. One could hope that 3D Doppler would add to more accurate diagnosis or at least shorten usually a long differential diagnosis list. Recent publications are certainly directed in this direction; however, when a new diagnosis modality is introduced into clinical practice, the pendulum usually swings from a very high optimism to the other side. Ultimately, it will get settled somewhere in the middle once many prospective studies are done and papers are published. One can still remember a similar story in early 1990s when transvaginal color Doppler was optimistically introduced into programs for early detection of ovarian cancer. We present most recent publications limited by a relatively small number of papers dealing with 3D Doppler and assessment of adnexal mass based on ultrasound criteria.

In their study, Kurjak et al. aimed to determine the diagnostic accuracy of 3D sonography and 3D power Doppler imaging, used together with standard 2D transvaginal gray scale and color/power Doppler modalities, for preoperative sonographic assessment of suspected ovarian lesions [11]. Five-year retrospective analysis was performed by their experts on ultrasonography and surgery on the reports from 43 referred patients with suspected stage-I ovarian cancer. All patients were evaluated during the week prior to surgery at our department. Preoperative sonographic assessment included careful examination of ovarian volume, morphology, and vascularity by four complementary sonographic methods. Scoring systems combining morphologic and Doppler parameters were adopted for 2D and 3D sonographic examinations. Final diagnosis was confirmed by a histopathologist. Of the 43 stage-I ovarian cancers, 42 cases were successfully detected preoperatively by four complementary sonographic methods. Only 30 (69.8%) and 37 (86.1%) cases of stage-I ovarian cancers were detected by 2D gray-scale and combined 2D gray-scale and color Doppler sonography, respectively. Morphologic analysis obtained by 3D sonography alone detected 32 of 43 ovarian malignancies, reaching a diagnostic rate of 74.4%. Qualitative analysis of tumor vascularity architecture by 3D power Doppler significantly improved the sonographic management process and successfully detected 41 cases of stage-I ovarian cancer (95.4%). When morphologic features obtained by 3D sonography were added to 3D power Doppler findings, we achieved an even higher diagnostic accuracy of 97.7%. The Zagreb group found a statistically significant difference in diagnostic rates of 3D power Doppler, and especially the combined use of 3D sonography and 3D power Doppler in comparison with those obtained with transvaginal 2D gray-scale or 3D sonography. They concluded that in comparison with transvaginal 2D gray-scale or 3D sonography, 3D power Doppler and especially the combined use of 3D sonography and power Doppler imaging significantly improve diagnostic accuracy in preoperative sonographic assessment of suspected ovarian lesions.
It appears that 3D sonography is a novel diagnostic method proposed to be an additional non-invasive tool in the assessment of ovarian tumors. Czekieradowski et al. also studied the diagnostic potential of 3D sonography and power Doppler in the preoperative differentiation of adnexal masses [12]. One hundred twenty-eight women with tumors thought to be of adnexal origin were examined preoperatively. Following morphologic (papillae, septa, tumor size, and volume) and color Doppler (PI, RI, Vmax, and TAMX) assessment, 3D Doppler ultrasound of adnexal tumors was performed. Various scanners were used and included: ATL 5000 HDI (Phillips, Bothell, Mass.) and Combi 350 and Voluson 750 (Kretztechnik, Austria) machines. The following variables were studied: inner wall structure; presence of papillae; thickening > 3 mm of septa as well as vascular branching pattern; number and localization of small blood vessels; and the presence of vascular anastomoses. Twenty-nine tumors were malignant (3 FIGO stage I) and 101 masses were benign. Power Doppler combined with 3D sonography predicted malignancy with a sensitivity of 92.6% (25 of 27 patients). Commonly used morphologic and Doppler criteria produced lower sensitivity, the values being in range of 45%–87.5%. Negative predictive value of 97.2% was the highest for 3D sonography. The authors concluded that the selective use of 3D ultrasound and power Doppler could be used to better characterize adnexal tumors. Detailed 3D sonography can help in identifying women who can have less invasive surgical procedures, if needed, such as laparoscopy, or be referred to a gynecologic oncologist.

Cohen and co-authors wanted to determine if 3D power Doppler ultrasound improves the specificity for ovarian cancer detection as compared with 2D ultrasound [13]. Seventy-one women with a known complex pelvic mass were referred for a preoperative ultrasound evaluation with both 2D and 3D gray-scale ultrasonography. The 3D studies were performed with the Kretz Voluson 530D using a mechanized transvaginal probe. Surface rendering and power Doppler imaging were performed by the same gynecologic sonologist and reassigned to one of four echo patterns: cystic; multicystic; complex; or solid. Sonographic criteria used for diagnosing ovarian cancer were based on a system that included morphologic characteristics, histologic prediction, and power Doppler imaging. Seventy-one women underwent surgical exploration: 14 (19.7%) had ovarian cancer (2 FIGO stage I, 2 stage II, 7 stage III, and 3 metastatic colon) and 2 had uterine cancer. Two-dimensional gray-scale ultrasound identified 40 masses as suspicious for cancer, including all 14 malignancies, yielding a sensitivity, specificity, and positive predictive value of 100%, 54%, and 35%, respectively; however, evaluation with 3D power Doppler identified only 28 cases as suspicious (including all 14 cancers), resulting in a sensitivity, specificity, and positive predictive value of 100%, 75%, and 50%, respectively. It was an obvious conclusion from this study that 3D power Doppler imaging better defines the morphologic and vascular characteristics of ovarian lesions. Both 2D and 3D imaging correctly identified all malignancies; however, the specificity significantly improved with the addition of 3D power Doppler. This improved diagnostic accuracy may promote improved patient care by separating complex benign masses from ovarian cancer, thereby facilitating appropriate physician referral.

In another study, the Zagreb group tried to determine whether 3D and 3D power Doppler can improve the ability to differentiate benign from malignant ovarian lesions [14]. Transvaginal ultrasound, transvaginal color Doppler, 3D US, and 3D power Doppler were performed on 90 patients with ovarian lesions during the week prior to surgery. Four independent sonographers were blinded to the results of other ultrasound studies. Color Doppler studies added to transvaginal gray-scale characterization of ovarian lesions resulted in sensitivity of 88.89 and specificity of 97.53% in diagnosing ovarian malignancy. Qualitative analysis of tumor vascularity by 3D power Doppler added to morphologic features obtained by 3D ultrasound was clinical pertinent and reached sensitivity and specificity of 100% and 98.76%, respectively. They concluded that 3D ultrasound and power Doppler can enhance and facilitate the morphologic and functional evaluation of both benign and malignant ovarian lesions. Introduction of the 3D quantitative technique for measurements of blood flow and vascularization may increase clinical relevance of these studies.

The same authors investigated the potential usefulness of contrast-enhanced 3D power Doppler sonography in the differentiation of benign and malignant adnexal lesions [16]. Thirty-one patients with complex adnexal lesions of uncertain malignancy at transvaginal B-mode and/or color Doppler sonography were prospectively evaluated with 3D power Doppler sonography before and after injection of a contrast agent. Presence of a penetrating pattern and a mixed penetrating and/or peripheral pattern suggested adnexal malignancy. The results were compared with histopathologic findings. There were 10 cases of ovarian malignancy and 21 benign adnexal lesions. Of 10 ovarian cancers, 6 showed vascular distribution suggestive of malignancy at non-enhanced 3D power Doppler sonography. After injection of contrast agent, a penetrating vascular pattern and/or mixed penetrating and peripheral pattern were detected in all cases of ovarian malignancy as well as in
two benign lesions (fibroma and cystadenofibroma), which were misdiagnosed as malignant. The use of contrast agent with 3D power Doppler sonography showed diagnostic efficiency of 96.7%, superior to that of non-enhanced 3D power Doppler sonography (93.5%). The study conclusion was that contrast-enhanced 3D power Doppler sonography provides better visualization of tumor vascularity in complex adenexal masses. If used together with 3D morphologic ultrasound assessment, enhanced 3D power Doppler imaging may precisely discriminate benign from malignant adenexal lesions.

It is well known that angiogenesis is a fundamental event in the growth of tumors as well as in physiologic conditions. In an ongoing prospective study involving eight women, Suren et al. investigated the microvasculature within the cervix by the use of 3D Power Doppler [16]. The ultrasound equipment was used in conjunction with specialized software providing high-resolution “3D angio mode.” The system provides the ability to visualize blood flow in small vessels that are undetectable by conventional color Doppler techniques and also to study the architecture and determine the number of blood vessels. Comparison of the vessels in the normal cervix with those in the cervix affected by carcinoma or bacterial or viral infection demonstrated that, in malignant tissue, there is a chaotic network of tortuous vessels traversing the tumor mass, whereas in benign tissue or tissue that is inflamed as a result of infection, the course of the vessels has a regular structure.

3D Doppler in Benign Gynecology

Recent developments in ultrasound have presented new opportunities for assessing tissue vascularity and blood flow with ultrasound. These new methods include 3D imaging, power Doppler sonography, and a variety of harmonic imaging techniques, ultrasound contrast agents, electronic compounding, and pulse-sequencing methods that improve the signal-to-noise relationship as well as structural conspicuity. By using these technologic advances, it is now possible to assess macroscopic blood flow in organs and tumors, and to assess changes in flow and vascularity that occur in response to therapeutic efforts.

It is obvious that technologic advances in ultrasonic imaging have revolutionized the management of women’s health care. Following the course, we also started to evaluate the clinical applications of 3D ultrasonography. Our study prospectively evaluated 161 obstetric and gynecologic patients [17]. Both 2D and 3D imaging data were acquired from real-time ultrasonography. Three orthogonal planes were displayed on a monitor and were used to create the rendered 3D images. Two hundred one 3D ultrasonographic studies were performed, 165 transabdominally and 36 transvaginally. Transabdominally, an average of eight acquisitions per patient were obtained. Of the clinically suspected abnormalities, 29 of 32 (91%) were confirmed by 3D imaging. Three of 32 (9%) improved the diagnostic capabilities or changed the diagnosis. Of the 36 transvaginal studies, an average of four acquisitions per patient were done. Thirty (83%) of these patients had suspected abnormalities and all were confirmed. We concluded that 3D ultrasonographic imaging appears to be highly promising in the clinical setting.

Recent advances in ultrasound technology have enabled the diagnosis of overall tissue vascularization by 3D power Doppler (Fig. 38.5). The published case report describes 3D power Doppler characteristics of unilateral ovarian torsion 2 weeks after embryo transfer in a pregnant patient with bilateral hyperstimulated ovaries [18]. Before laparoscopic treatment, the twisted right ovary showed the following 3D power Doppler indices: mean grayness index, 15.66; vascularization index, 0.24; flow index, 21.99; and vascularization flow index, 0.05. One hour after laparoscopic treatment, 3D power Doppler indices of the untwisted ovary were as follows: mean grayness index, 25.61; vascularization index, 3.81; flow index, 42.80; and vascularization flow index, 1.63. The resistance index of the ovarian vessels before and after laparoscopy showed no significant difference (5.1 vs 5.2). The diagnosis of ovarian torsion can be better made with 3D power Doppler sonography than with 2D Doppler sonography.

Skalkevicius et al. performed the study to evaluate the feasibility of 3D Doppler in the assessment of the patency of the Fallopian tubes during hysterosalpingo-contrast sonography (HyCoSy) [19]. Women attending the fertility clinic were offered a Fallopian tu-

![Fig. 38.5. Overall tissue vascularization of the enlarged ovary as assessed by 3D power Doppler](image-url)
bal patency test as part of the initial investigation. Hysterosalpingo-contrast sonography using contrast medium Echovist was performed in 67 women. Findings on 2D gray-scale scanning and 3D power Doppler imaging were compared. The first technique visualizes positive contrast in the Fallopian tube; the second demonstrates flow of medium through the tube. Contrast medium Echovist produced prominent signals on the 3D Doppler image. Free spill from the fimbrial end of the Fallopian tubes was demonstrated in 114 (91%) tubes using the 3D Doppler technique and in 58 (46%) of tubes using conventional HyCoSy. The mean duration of the imaging procedure was less with 3D Doppler, but the operator time that included post-procedure analysis of the stored information was similar. A significantly lower volume of contrast medium (5.9 ± 0.6 ml) was used for 3D Doppler in comparison with that (11.2 ± 1.9 ml) used for conventional 2D HyCoSy. The authors concluded that 3D Doppler with surface rendering allowed visualization of the flow of contrast through the entire tubal length and free spill of contrast was clearly identified in the majority of cases. The 3D Doppler method appeared to have advantages over the conventional HyCoSy technique, especially in terms of visualization of spill from the distal end of the tube, which was achieved twice as often with the 3D technique. Although the design of the investigation did not allow the side effects of the two techniques to be compared, the shorter duration of the imaging and lower volume of the contrast medium used suggested that the 3D Doppler technique might have a better side-effect profile. This technique allowed better storage of the information for re-analysis and archiving than conventional HyCoSy.

Whether salpingectomy affects ovarian function is controversial. In Chan's et al. study, ovarian function was assessed by antral follicle count, ovarian volume, and ovarian stromal blood flow measured by 3D power Doppler ultrasonography [20]. The objectives of the study were to compare the ovarian function of the surgically treated side with the non-surgically treated side after unilateral salpingectomy performed through laparoscopy or laparotomy for ectopic pregnancy. Thirty-two patients with unilateral salpingectomy performed for ectopic pregnancy were recruited: 18 through laparoscopy and 14 through laparotomy. Ultrasound scans were performed in the early follicular phase. Ovarian volume, antral follicle count, and 3D power Doppler indices were comparable between the surgically treated and the non-surgically treated side in the whole group and in the laparotomy group. The antral follicle count and 3D power Doppler indices were significantly reduced on the surgically treated side in the laparoscopy group. Based on this study, ovarian function seems to be impaired after laparoscopic unilateral salpingectomy at short-term assessment.

Three-dimensional ultrasound, as any ultrasound image, is not immune from artifacts. Nelson and co-authors wanted to increase awareness of clinicians and sonographers with respect to common 3D ultrasound artifacts and to use this increased awareness to avoid or reduce the occurrence of misdiagnosis in clinical practice [21]. Patient 3D ultrasound data were acquired using several different scanners and reviewed interactively on the scanner and graphics workstations. Artifacts were catalogued according to artifact origin. Two-dimensional ultrasound (2D US) artifacts were classified whether they were of a B-mode or color/power Doppler origin and their presentation in the original scan planes and the resulting volume re-sliced planes and rendered images was identified. Artifacts unique to 3D US were observed, noted, and catalogued on the basis of whether they arose during acquisition, rendering, or volume-editing operations. Acoustic artifacts identified included drop-out, shadowing, etc., the presentation of which depended on the relationship between slice and imaging plane orientation. Color/power Doppler artifacts were related to gain, aliasing, and flash which could add apparent structure or confusion to the volume images. Rendered images also demonstrated artifacts due to shadowing and motion of adjacent structures, cardiac motion or pulsatility of the cardiac septum, or vessel walls. Editing artifacts potentially removed important structures. Three-dimensional ultrasound is prone to the same types of artifacts encountered in 2D US imaging plus others unique to volume acquisition and visualization. The consequences of these diagnostically significant artifacts include mimicking of abnormal development, masses, or missing structures thus requiring careful study before reaching a diagnosis.

The 3D reconstruction of ultrasound images has become a widespread option in ultrasound equipment. Specific softwares have become available and 3D reconstruction feasible since the early 1990s, particularly since 1994. Several clinical applications are feasible in some parenchymatous organs (such as uterus or ovaries), hollow pelvic masses (e.g., ovarian cysts), peripheral vessels (uterine artery and branches), and new-formed vessels (e.g., tumor neo-vascularization) or ectopic pregnancy. Moreover, tumoral vessels in pelvic organs can be reconstructed (Fig. 38.6). The introduction of echocontrast agents and second harmonic imaging has permitted study of normal and abnormal peripheral, central, and parenchymatous vessels, with patterns similar to those obtained with digital angiography. The spatial relationships between the vascular structures of the uterus, ovaries, and Fallopian tubes were studied with 3D Doppler ultrasound (Fig. 38.7). The applications
of this new technique include the analysis of vascular anatomy and the potential assessment of organ perfusion. The latest application is intra-vascular study. Some catheters with an ultrasound transducer in the tip have been tested for intra-vascular studies. Just like conventional transducers, they provide 2D images which are then postprocessed into longitudinal 3D or volume reconstructions. The former resemble angio-

graphic images and can be viewed 3D rotating the image along its longitudinal axis. Volume images, which are more complex and slower to obtain, can be rotated on any spatial plane and provide rich detailing of the internal vascular lumen. The clinical importance of intravascular ultrasound with 3D volume reconstructions lies in the diagnosis of vascular conditions and the assessment and monitoring of intravascular interventional procedures, e.g., to detect inaccurate deployment of intravascular stents and endoluminal grafts during the maneuver. Three-dimensional reconstructions involve geometric data assembly and volumetric interpolation of a spatially related sequence of tomographic cross sections generated by an ultrasound catheter withdrawn at a constant rate through a vascular segment of interest, resulting in the display of a straight segment; therefore, particular care is needed and there are some useful hints to avoid mistakes.

Three-dimensional reconstructions of B-mode and Doppler images are no longer a work in progress and their clinical importance and possible applications are both established and ever-increasing. On the
other hand, independent of the different types of energy used, also computed tomography and magnetic resonance 3D reconstructions are very useful from a clinical viewpoint and they have become an established routine technique for both these methods. It is very likely that 3D volume reconstructions in ultrasound will find numerous applications in the near future (Fig. 38.8). They may help to increase the diagnostic confidence and to facilitate diagnosis, intra-procedure monitoring in interventional radiology, and follow-up and also to reduce the number of invasive examinations with iodinated contrast agents.

Conclusion

At this point in time, the clinical application of 3D Doppler ultrasound is likely to advance rapidly, as improved 3D rendering technology becomes more widely available. In the past 10 years, gynecological ultrasonography has proliferated rapidly, and is by some gynecologists considered an integral part of the gynecological exam. Abnormalities are detected in asymptomatic women at a high rate, resulting in a number of surgical interventions due to suspected malignancy. Present evidence is insufficient to determine the medical and economical value, if any, of surgical removal. Such intervention may be in fact be as detrimental as leaving an abnormality in place. Gynecologic ultrasonography should therefore be performed on strict medical indications. Proper training of operators is also vital. In the past decade, research investigators and commercial companies have further advanced ultrasound imaging with the development of 3D ultrasound. This new imaging approach is rapidly achieving widespread use with numerous applications in human reproduction, gynecologic oncology, and benign gynecology. The major reason for the increase in the use of 3D ultrasound is related to the limitations of 2D viewing of 3D anatomy, using conventional ultrasound. This occurs because:

1. Conventional ultrasound images are 2D, yet the anatomy is 3D; hence, the diagnostician must integrate multiple images in his mind. This practice is inefficient, and may lead to variability and incorrect diagnoses.
2. The 2D ultrasound image represents a thin plane at some arbitrary angle in the body. It is difficult to localize the image plane and reproduce it at a later time for follow-up studies.

Three-dimensional Doppler ultrasound is a new modality finding its way into clinical practice. Most of the major ultrasound vendors are now developing 3D ultrasound capabilities. We expect that, although 3D ultrasound will not replace 2D ultrasound, many additional benefits will be identified and its use will continue to grow, especially when 3D Doppler is used. The ability to evaluate pelvic anatomy, pathology, and blood flow with multiplanar and surface-rendered images provides physicians additional valuable clinical information. Volume data allows for a specific point in space to be evaluated from many different orientations by rotating, slicing, and referencing the slice to other orthogonal slices. It also allows for new volume-rendering displays that show depth, curvature, and surface images not available with conventional methods. The current limitations of image resolution, intuitive interfaces for obtaining and displaying optimal images, and technologic limitations for data storage and manipulation (including real-time 3D ultrasound) will surely be overcome in the near future. As 3D Doppler ultrasound continues to develop, the presence of real time 3D (or 4D) imaging equipment in the clinical setting will expand and stimulate new areas of investigation and identify new frontiers where 3D ultrasound can further enhance clinical care.

References

Doppler Ultrasound: A Good and Reliable Predictor of Ovarian Malignancy

Shah Dharita · Shah Sandip · Parikh Jay · Bhatt C. J. · Vaishnav Kavita · Bala D. V.

Received: 15 May 2012 / Accepted: 23 September 2012 / Published online: 10 November 2012

Abstract

Aims The aim of the present study was to prove the efficiency of Color Doppler and Spectral Doppler in evaluation and characterization of the ovarian neoplasm. Materials and Methods In total, 104 patients with adnexal masses were examined sonographically to evaluate for morphologic characteristics, as well as pulsatility indices (PI), and resistance indices (RI) over a period of 2 years, of which 20 were excluded as the masses were not finally proven to be adnexal, and thus 84 patients with ovarian neoplasm were retained as the study subjects. The final diagnosis was based on histopathologic confirmation. Result Out of 84 cases, 44 were benign and 40 were malignant. Color Doppler showed vascularity in 97.5 % of malignant tumors in contrast to only 68.1 % of benign tumors. The present study showed that, 87.5 % of malignant tumors had PI less than 0.8 in contrast to only 4.54 % of benign tumors. Similarly, 82.5 % of malignant tumors had RI less than 0.6 in contrast to only 6.81 % of benign tumors. Conclusion Multiparameter analysis utilizing B-mode USG along with Color Doppler and Spectral Doppler is the mainstay in diagnosis of patients with ovarian tumors. A good specificity (84.1 %) and sensitivity (97.5 %) with PI and RI values of 1.0 and 0.6, respectively, was achieved with the present study which is highly significant in differentiating between malignant and benign ovarian tumours.

Keywords Doppler indices · Ovarian malignancy

Introduction

Adnexal masses pose a special diagnostic challenge and suspicion for malignancy is based largely on imaging appearance. The ovarian malignancy is the third leading cause of cancer in females in population based cancer registry of Ahmedabad district (year 2009). Therefore early diagnosis and management of ovarian tumors has significant clinical importance. Effective evaluation of ovarian malignancy using Color and Spectral Doppler has been a subject of challenge as its implication. The present study aimed at assessing and differentiating benign and malignant ovarian neoplasms with
the help of B-mode ultrasonography in conjunction with Color Doppler and Spectral Doppler and to correlate the imaging findings with histopathologic findings. The newly formed tumoral vessels are devoid of muscular layer, have low impedance-high velocity flow, and thus the resistance measured by color flow indices such as resistance indices ($RI$) and pulsatility indices ($PI$) are low, which can be used as predictors of ovarian malignancy.

**Study Design**

In a study period of 2 years, a total of 104 patients were prospectively evaluated by B-mode ultrasonography, Color and Spectral Doppler study using a TOSHIBA NEMIO XG real-time Ultrasound and Doppler Scanner through a transabdominal approach, using a 3.75-MHz sector transducer. If required, transvaginal sonography was also performed with a 6.0-MHz endovaginal transducer. The study included the patients who were referred with an adnexal mass with age group between 40 and 60 years. Patients excluded from the study were those having anechoic cyst which resolved on follow-up study, patients with pelvic mass of uterine origin determined either per-operatively or on histopathology report, and those who were lost to follow-up. Written informed consent was taken from all of these patients. Initially, the patients were subjected to B-mode USG. Color Doppler study with no aliasing along with pulsed Doppler at the lowest pulse repetition frequency and at high sensitivity settings was then undertaken. The pulsed Doppler waveform analysis was done. The lowest values of $PI$ and $RI$ were recorded from three different readings that were measured. These indices were correlated with histopathologic reports. The sensitivity and specificity of various cutoff levels of $PI$ and $RI$ were calculated, and the proper values of $PI$ and $RI$ for differentiating the tumors were determined by calculation of area under each receiver operator characteristic curve.

**Results**

Out of a total of 104 patients examined over a period of 2 years, 20 were excluded from the study group as six patients were diagnosed to have mass of uterine origin on B-mode USG; seven patients with adnexal masses did not undergo histopathology examination and thus were not followed up; two patients had mass of uterine origin on HPE; and five patients were having unilocular ovarian cysts, which resolved on follow-up USG. Thus, the study group was composed of 84 patients with ovarian neoplasms. Color Doppler showed neovascularity in 97.5 % of malignant tumors in contrast to only 68.1 % of benign tumors (Table 1). Absent blood flow in a solid tumor almost always ruled out the possibility of malignancy. In the present study, 87.5 % of malignant tumors had $PI > 0.8$ in contrast to only 4.54 % of benign tumors. Similarly, 82.5 % of malignant tumors had $RI > 0.6$ in contrast to only 6.81 % of benign tumor (Table 2). B-mode USG alone correctly diagnosed benign tumors in 20 patients, while B-mode along with Color Doppler and Spectral Doppler helped us to diagnose 37 benign tumors out of a total of 44 patients having benign neoplasms. Similarly, 35 patients with malignancy were correctly diagnosed on B-mode USG alone, while with help of Color and Spectral Doppler in conjunction with B-mode USG, 39 patients were correctly diagnosed to have malignant ovarian tumors (Table 3).
Discussion

USG, because of being relatively inexpensive, noninvasive, and widely available, is considered to be the method of choice of investigation in the initial evaluation of suspect adnexal masses. Transabdominal USG, and/or endovaginal USG, should be performed for the evaluation of adnexal masses [1, 2]. Color Doppler with spectral analysis using indices such as $PI$ and $RI$ is of immense value in yielding better characterization of ovarian neoplasm. It is factually correct that low impedance to blood flow with high velocity is suggestive of malignancy, whereas moderate-to-high impedance to blood flow is correlated to benign tumors. Resistive indices less than 0.4–0.8 [3, 5] and pulsatility indexes less than 1.0 are generally considered to be suspicious for malignancy [3–6]. In the present study, $PI<0.8$ and $RI<0.6$ were considered for analysis. B-mode features suggestive of malignancy were also studied using a morphologic scoring system described earlier [7]. Color Doppler evaluation of the tumor showed the presence of neovascularity in 97.5 % of malignant tumors in contrast to 68.1 % benign tumors. Vascularity in cystic lesions was seen equally in septae as well as in wall, but in solid malignant tumors, the central vascularity was observed in 87.5 % cases and peripheral vascularity in 37.5 % cases. These findings were correlated well with the study by Valentin et al. [8] and Kurjak et al. [7], but the study by Sharon Stein et al. [9] suggested that internal color flow cannot be used as a predictor of malignancy (PPV 49 %), but the absence of color flow suggested benignity (NPV 94 %).

Neovascularization in tumor always offers lower resistance to blood flow in malignant neoplasm (Figs. 1, 2, 3). The present study was based on a pre-established cutoff criterion of $PI<0.8$ and $RI<0.6$ as described by Jonathan Carter et al. [10]. Using the cutoff criterion of $PI<1.0$ and $RI<0.4$, Kurjak et al. [7] achieved high sensitivity and specificity as the study group comprised only postmenopausal women.

| Table 1: Comparison of cutoff criteria for $PI$ value of the present study between criteria of $PI<0.8$ and $PI<1.0$ to diagnose ovarian malignancy |
|-------------|-----------------|-----------------|
|             | $PI<0.8$ (%)    | $PI<1.0$ (%)    |
| Sensitivity | 87.5            | 93              |
| Specificity | 95.4            | 93              |
| Positive predictive value | 94.5 | 93 |
| Negative predictive value | 89.3 | 93 |

| Table 2: Comparison of cutoff criteria for $RI$ value of the present study between criteria of $RI<0.6$ and $RI<0.4$ to diagnose ovarian malignancy |
|-------------|-----------------|-----------------|
|             | $RI<0.6$ (%)    | $RI<0.4$ (%)    |
| Sensitivity | 83              | 20              |
| Specificity | 93              | 98              |
| Positive predictive value | 92 | 89 |
| Negative predictive value | 85 | 58 |

<p>| Table 3: Sensitivity, specificity, positive predictive value, and negative predictive value of B-mode only and B-mode with color flowmetry and pulse wave study for patient with malignant ovarian tumor |</p>
<table>
<thead>
<tr>
<th>Diagnosis of malignant ovarian tumor</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-mode scan</td>
<td>87.5</td>
<td>45.45</td>
<td>61.4</td>
<td>80</td>
</tr>
<tr>
<td>B-mode with color flowmetry and pulse wave study</td>
<td>97.5</td>
<td>84.1</td>
<td>84.78</td>
<td>97.4</td>
</tr>
</tbody>
</table>
The present study, with PI 0.8, observed 87.5% of malignant tumors in contrast to only 4.54% of benign tumors (Table 1). Similarly, with RI 0.6, it observed 82.5% of malignant tumors in contrast to only 6.81% of benign tumors (Table 2). Extrapolating the data of the present study using the criterion PA 1.0 and 0.4 proposed by Kurjak et al. [7] and Buy et al. [11], 92.5% of malignant tumors and 6.82% of benign tumors showed PA 1.0, while only 20% malignant tumors and 2.27% of the benign tumors showed RI 0.4. As elucidated previously by many authors [12, 13], the absence of vascularity is always indicative of benignity (Fig. 4). In the present study, B-mode USG achieved a sensitivity of 87.5%, a specificity of 45.45%, and a PPV of 61.4%, but when the pulsatility and resistance index was included, more acceptable levels of sensitivity at 97.5%, specificity at 84.1%, and positive predictive value at 84.78% were obtained. These results correlate well with a study by Timor-Tritsch et al. [14].
Thus, the present study data were rendered slightly more specific and less sensitive with $RI \leq 0.4$ and more sensitive and specific with $PI \leq 1.0$, and hence, to optimize sensitivity and specificity, $PI \leq 1.0$ and $RI \leq 0.6$ should be taken. In the present study, B-mode USG along with Color Doppler and Spectral Doppler offers reliable prediction of benignity of tumor as only 4.54% benign tumors were misdiagnosed in contrast to 17.5% of malignant tumors. This feature correlates well with the study by Stein et al. [9]. Only after when Color Doppler showed intratumoral vascularity (mainly central) and Spectral Doppler showed low resistance velocity waveforms in intratumoral vessels, the definite diagnosis of malignancy in solid tumors was made (Fig. 5). Fairly good specificity and sensitivity (Table 3) with $PI$ and $RI$ values of 1 and 0.6, respectively, were achieved in the present study [15]. Thus, multiparameter analysis utilizing B-mode gray scale USG along with Color and Spectral Doppler offers good sensitivity, specificity, and positive predictive value. It should always be the diagnostic modality of choice for the patients with adnexal masses to establish the diagnosis.
of ovarian malignancy.

Shah D. (8), Associate Professor _ Parikh J.,
3rd year Resident _ Bhatt C. J., Associate Professor_
Vaishnav K., Assistant Professor
Department of Radiology, VS Hospital, Ellisbridge,
Ahmedabad 380006, India
e-mail: dharsan19@gmail.com
Shah S., Consultant Gynecologist
Department of Gynecology, SAL hospital, Thaltej, Ahmedabad, India
Bala D. V., Professor
Department of Preventive and Social Medicine, VS Hospital,
Ellisbridge, Ahmedabad 380006, India

References
Whither the annual bimanual pelvic examination?

The absence of evidence for benefit is not the same as evidence of absence of benefit.

August 01, 2014

By Charles J. Lockwood, MD, MHCM

Dr. Lockwood, Editor-in-Chief, is Dean of the Morsani College of Medicine and Senior Vice President of USF Health, University of South Florida, Tampa. He can be reached at DrLockwood@advanstar.com.

Recently, Qaseem and colleagues published an American College of Physicians (ACP) Clinical Guideline advising against pelvic examinations for the detection of pathological conditions in asymptomatic, nonpregnant, adult women.¹

This advisory has generated much commentary in the blogosphere and particularly among ob/gyns. Many women, upon hearing news reports concerning the ACP guidelines, will assume these recommendations are valid and that they no longer need annual pelvic exams. Moreover, some women may assume that since they no longer need such an exam, they also will not need to see their gynecologist annually.

When added to the confusion already rampant as to the need for mammograms and Pap smears, this ACP guideline will add yet another barrier to our ability to provide appropriate preventative care to our patients.
Are screening pelvic exams needed?

The Qaseem et al. study was a literature review conducted by the Minneapolis Veterans Affairs Health Care System’s Evidenced-based Synthesis Program center. The authors sought to assess the accuracy, benefits, and harms of screening pelvic examinations. They defined a pelvic exam as a “combination” of speculum and bimanual examination not including cervical cancer screening.

For this purpose, the authors conducted a MEDLINE search of relevant articles addressing these questions published from 1946 to 2014. Based on their findings, the ACP strongly recommended “against performing screening pelvic examinations in asymptomatic, non-pregnant, adult women” based on “moderate-quality evidence.” Potential harms cited included unnecessary laparoscopies or laparotomies, fear, embarrassment, anxiety, pain or discomfort and, ironically, avoidance of necessary care.

While I do believe there is a place for evidence-based medicine and I strongly support thoughtful, comprehensive, and data-rich analyses whose conclusions have robust statistical support, this study had none of those elements.

First the authors focused only on ovarian cancer and detection of bacterial vaginosis because those were the only conditions about which there were sufficient published data to draw tangential conclusions. (What is the old line about the inebriated fellow looking for his keys under the lamp post because that is where the light is shining?) As such, the authors failed to address the myriad of other reasons ob/gyns carry out bimanual exams, such as for detection of myomas, evidence of pelvic relaxation and stress incontinence, signs of endometriosis, chronic pelvic inflammatory disease, cervical polyps, vaginal cysts, etc. Indeed the authors report that no studies directly address the utility of pelvic exams for any of these conditions. They also note that no studies have evaluated the potential indirect benefit of annual pelvic exams on non-ovarian and non-cervical cancer morbidity or mortality. Furthermore, they point out that no studies have evaluated the potential benefit of such exams as an incentive for women to access care and receive “recommended gynecological services, such as contraception, screening for sexually transmitted infections and other non-gynecological care.”
The authors further admit that no studies actually address potential harms such as false reassurance, over-diagnosis, over-treatment, and diagnostic procedure-related harms even though these were the reasons they recommended against routine pelvic examinations! And they admit that studies examining pain, embarrassment, and fear are of low quality. Yet they confidently conclude that “current evidence shows that harms outweigh demonstrated benefits associated with the screening pelvic examination.”

The American College of Obstetricians and Gynecologists (ACOG) quickly responded to this ACP recommendation by directing providers to its “Well-Woman Visit” committee opinion. This guideline recommends annual pelvic examinations for patients 21 years of age or older, noting that “this recommendation is based on expert opinion, and limitations of the internal pelvic examination should be recognized.”

ACOG also noted that “the decision whether or not to perform a complete pelvic examination at the time of the periodic health examination for the asymptomatic patient should be a shared decision after a discussion between the patient and her health care provider.” This is a far more reasonable position to hold since the absence of evidence for benefit is not the same as evidence of absence of benefit! I am frankly astonished at the certainty of the ACP conclusion.

**Should a vaginal ultrasound be added to annual bimanual examination?**

When faced with recommendations to change long-established practice based on preliminary, tentative, or frankly flimsy evidence, it is customary to recommend that large clinical trials be undertaken to permit a consensus. But in my opinion, in this case, that would be a waste of time.

My position is that the bimanual exam, while useful, is not sufficient to allow for an optimal contemporary assessment of reproductive tract pathology. Instead I would suggest that we ob/gyns double down on the utility of such exams by adding a vaginal ultrasound, performed at no cost, to annual bimanual exams.

How long did it take physicians to stop listening to patients’ hearts with their ear on the chest wall after René Laennec invented the stethoscope? Yet we are still performing this relatively crude bimanual evaluation when we can carefully assess the anatomy of the
ovaries, tubes, myometrium, endometrium, and cervix in great detail and with astonishing clarity regardless of a patient’s body habitus. For two decades I have worked at institutions that have trained residents in both obstetrical and gynecological ultrasound. Multiple generations of practitioners are now extraordinarily adept at gynecological ultrasound. When cost is eliminated from the equation, the net potential benefit of this approach is substantial.

**Evidence for the efficacy of gyn ultrasound**

I am not the first to advocate for use of vaginal ultrasound as part of a routine gynecological examination. My colleague Dr. Steven Goldstein at New York University has been advocating for it for years.³ It has obvious utility in differentiating suspicious from benign cysts or myomas from ovarian pathology when a mass is suspected on bimanual examination.

The utility of ultrasound in assessment of abnormal endometrial bleeding is obvious. It can be used to longitudinally track the growth of myomas or identify early evidence of endometrial hyperplasia. Nevertheless, the pelvic exam still provides invaluable information about pelvic pathophysiology including the presence of pelvic organ prolapse. Detection of utero-sacral nodularity or a fixed retroverted uterus can help identify endometriosis. Vaginal pathology is also often better detected with a bimanual exam. As noted, because my proposal is not to charge the patient for such an ultrasound, cost would not be a factor. The only concern would be overdiagnosis and excessive interventions for benign lesions. The harm accruing such “false positives” would have to be weighed against the benefits of early detection of endometriosis, polyps, hyperplasia, myomas, adenomyosis, and incidentally detected endometrial and ovarian cancers. Thus, randomized trials would indeed be in order.

**Take-home message**

The ACP’s Clinical Guideline advising against pelvic examinations for the detection of pathological conditions in asymptomatic, nonpregnant, adult women is unfounded, ill timed, and ill considered. It is at best premature and non-evidence-based; at worst it will dissuade women from seeking appropriate preventative care and may be harmful. The ACOG guideline recommending annual pelvic examinations for patients 21 years of age or older
should continue to be followed. Moreover, the utility of adding a no-cost vaginal ultrasound to such exams should be studied. Comparative effectiveness research is under assault from conservative members of Congress\textsuperscript{4} and studies such as that of Qaseem and colleagues will give these critics fresh ammunition.

References


Stage I ovarian cancer by transvaginal color Doppler sonography: a report of 18 cases

A. Kurjak, H. Shalan, R. Matijevic, M. Predanic and S. Kupesic-Urek

Ultrasound Institute, School of Medicine, University of Zagreb, Croatia

Key words: OVARIAN CANCER, TRANSVAGINAL SONOGRAPHY, COLOR FLOW IMAGING, PULSED DOPPLER

ABSTRACT

A total of 18 cases with ovarian carcinoma stage I (15 stage Ia and three stage Ib) were studied retrospectively to evaluate the efficiency of transvaginal color Doppler sonography in detecting the disease in its early stages. Four asymptomatic women (two cases with morphologically normal ovaries, and two with simple unilocular cysts) were found during the screening program. These cases would have been missed without the use of transvaginal color Doppler sonography. One ovary with stage Ia, and another ovary in a case with stage Ib ovarian cancer were missed. These data show the ability of transvaginal color Doppler sonography to detect ovarian cancer as early as stage I even in asymptomatic women as well as in the morphologically normal ovary.

INTRODUCTION

Ovarian cancer is the most common cause of death resulting from gynecological malignancy. About 22,000 women in the USA alone will develop the disease every year. As the disease has no characteristic symptoms in its early stages, most of the cases are diagnosed during the advanced stages where the 5-year survival rate is very low.

Until now, the diagnosis of ovarian cancer during its early stages was a matter of chance, rather than as a result of a scientific approach. It has been estimated that the 5-year survival rate of stage I ovarian cancer is as high as 90%. If the number of early-stage diagnoses could be increased by 80%, the mortality rate from ovarian cancer would decrease by one-half.

A non-invasive diagnostic method which is able to detect the early stages of ovarian cancer is, therefore, urgently required. Transvaginal color Doppler sonography is a recent development among the current diagnostic imaging modalities. Several studies have shown its capabilities to discriminate between benign and malignant neoplasms; the technique is non-invasive, and can be used in the early as well as in the late stages of ovarian cancer. If these data prove significant, the technique could form the basis of a screening method for a population-based program for the early detection of ovarian cancer.

The aim of the work, presented here, is an evaluation of morphological and blood flow characteristics of stage I ovarian carcinoma detected by transvaginal color and pulsed Doppler sonography via a retrospective study.

SUBJECTS AND METHODS

During the last 3 years, 18 cases of ovarian carcinoma FIGO stage I were diagnosed and managed in our Institute. The clinical and color Doppler data, operative staging, and histopathological reports of these 18 cases were collated retrospectively.

The machines used in this study were UM9 (Advanced Technology Laboratories, USA) and SSD-680 (Aloka Co., Japan), both with 5 MHz transvaginal transducers. The transvaginal color Doppler examination technique is similar to that described in previous studies. The B-mode was used to evaluate the morphology of both ovaries, and then color flow imaging was superimposed to detect vascularized areas. Finally, pulsed Doppler was used to analyze blood velocity in the area of interest, and the Poulcerot resistance index (RI) was calculated to quantify the impedance to blood flow, as we have shown this to be superior to the pulsatility index. The average time of each investigation is usually 15-20 min; however, for suspicious cases the examination may take longer and a second opinion may be sought from another investigator.

The 18 cases were treated by the same surgical team; the FIGO classification for ovarian cancer staging, and the WHO recommendation for histopathological diagnosis were used.
Table 1  Menopausal status and age of patients with stage I ovarian carcinoma

<table>
<thead>
<tr>
<th>Menopausal status</th>
<th>n</th>
<th>%</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenopausal</td>
<td>5</td>
<td>28</td>
<td>39</td>
<td>27-50</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>13</td>
<td>72</td>
<td>57</td>
<td>49-67</td>
</tr>
</tbody>
</table>

Table 2  Clinical presentation of patients with stage I ovarian carcinoma

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>Pain</td>
<td>9</td>
<td>50</td>
</tr>
<tr>
<td>Bleeding</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Infertility</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 3  Sonographic patterns in stage I ovarian cancer

<table>
<thead>
<tr>
<th>Sonographic patterns</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal morphology</td>
<td>2</td>
</tr>
<tr>
<td>Cystic</td>
<td></td>
</tr>
<tr>
<td>unilocular</td>
<td>2</td>
</tr>
<tr>
<td>multilocular</td>
<td>7</td>
</tr>
<tr>
<td>Cystic (solid)</td>
<td>3</td>
</tr>
<tr>
<td>Solid</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
</tr>
</tbody>
</table>

Table 4  Pathology, staging, and resistance index in the studied group

<table>
<thead>
<tr>
<th>Pathology</th>
<th>n</th>
<th>Stage</th>
<th>Resistance index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary cystadenocarcinoma</td>
<td>12</td>
<td>Ia</td>
<td>0.39 0.01</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>4</td>
<td>Ia</td>
<td>0.37 0.03</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>1</td>
<td>I</td>
<td>0.43</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>1</td>
<td>I</td>
<td>0.29</td>
</tr>
</tbody>
</table>

RESULTS

This retrospective study was carried out on 18 cases with ovarian carcinoma stage I. A total of 15 cases were stage Ia and three were stage Ib. Five women were premenopausal and 13 postmenopausal, the mean and age ranges are shown in Table 1.

Four patients were asymptomatic and self-referred for their annual check-up. Two young patients, aged 27 and 29 years, were attempting conception and were detected during the period of the study (Table 2).

Two cases with morphologically normal ovaries, and another two with simple unilocular cysts were detected during our screening program. The other sonographic patterns are shown in Table 3.

Ovarian carcinoma stage I was detected in two normal-sized ovaries only from the color and pulsed Doppler signals, which represent tumor angiogenesis, and low impedance to blood flow calculated from Doppler waveform analysis; both were in postmenopausal women, and the largest diameter of each ovary was less than 3 cm. One of these ovaries showed anaplastic carcinoma, and the other showed adenocarcinoma of the ovary. Five cases were detected with enlarged ovaries (less than 5 cm in their largest diameter).

The tumor size ranged from 25 mm up to 84 mm in the largest diameter, with a mean value of 42 mm (± 11 mm). The visualization of abnormal vasculature within and/or around the tumors was 94% (17/18); the resistance indices were equal to or below 0.41. The correlations between the pathology, operative staging, and blood flow visualization with the mean resistance index are shown in Table 4. An illustrative example is shown in Figures 1-4.

One ovary with stage Ia, and another ovary in a case with stage Ib were missed using the transvaginal color Doppler technique, as it was impossible to detect vascularization. Both had a cystic sonographic pattern.

DISCUSSION

Although there is little doubt concerning the importance of early detection of ovarian cancer, the optimal screening method for this disease remains uncertain. The ideal screening test is expected to produce a shift towards early detection of ovarian cancer and would reduce the mortality from the disease.

To the best of our knowledge this is the largest series studying the role of transvaginal color Doppler sonography in stage I ovarian cancer. All the cases were managed by conventional surgical intervention; so far, the patients are in good health without any evidence of recurrence. These results could highlight the importance of diagnosing ovarian carcinoma as early as stage I in order to improve the patient's chances of survival and wellbeing.

The four asymptomatic cases were picked up by the screening program conducted by our institute; this is an important requirement for an ideal screening test which should detect the disease in asymptomatic women.

The phenomenon of tumor angiogenesis, which is essential for tumor growth, was first described by Folkman11 and proved by several studies12. Tumor angiogenesis constituted the basis for evaluating tumors in this study. This angiogenesis can be demonstrated by color flow imaging and quantified by impedance to blood flow13,14. To avoid false-positive findings of angiogenesis in the corpus luteum, premenopausal women should be examined during the 3-8th day of their menstrual cycle. It was possible to detect two cases with normal-sized ovaries and five cases with enlarged ovaries (< 5 cm), depending only on the presence of abnormal vasculature within and/or around the tumor with low impedance to blood flow. Ovarian cancer stage I was also discovered in morphologically-normal ovaries as well as in simple unilocular cysts which would have been missed if the morphology alone was considered. This finding could have an important clinical implication as a morphologically-normal ovary detected using B-mode
sonography is not always innocent, and a color Doppler examination is, therefore, mandatory to rule out malignancy.

CONCLUSION

Transvaginal color Doppler sonography is capable of detecting ovarian carcinoma as early as stage I. Furthermore, it has proved its potential in detecting the disease in asymptomatic women, as well as in women with normal-sized ovaries.

These results could justify its use as a routine test in annual check-ups; its use would be particularly justified in women at high risk.

REFERENCES

9. Thompson, R. S., Trudinger, B. J. and Cook, C. M. (1988). Doppler ultrasound waveform analysis: A/B ratio, pulsatil-


The Role of 3D Ultrasound and 3D Power Doppler Imaging in the Diagnosis and Evaluation of Ovarian Cancer: New Perspectives

MT Redondo, I Orensanz, FJ Salazar, S Iniesta, B Bueno, T Perez-Medina, JM Bajo
HU Santa Cristina, Madrid, Spain

Correspondence: Teresa Redondo Martín. Servicio de Ginecología, HU Santa Cristina
c/Maestro Vives, 2. 28009. Madrid, Spain
E-mail: tere_redondo@hotmail.com

BACKGROUND

Ovarian cancer is in frequency the third cancer of female genital tract, after those of uterus and cervix. However, its mortality is greater, and this is basically due to the difficulty in its early diagnosis, because it does not usually show symptoms until advanced stages and risk factors to develop it are unknown. A 3000 new cases of ovarian cancer are diagnosed a year, and practically 80% of women are diagnosed in advance stages (III or IV), with a resultant overall five-year survival rate of approximately 20%. The current diagnostic orientation of ovarian cancer is essential, not only for the repercussion the moment of the diagnosis has in the survival rates, but for the necessity of a correct planning in clinical conduct, referring the patient to specialized centers, and the necessity of a correct planning of a ruled radical surgery of ovarian cancer (surgical times, surgeon, etc.). Habitually, diagnosis of adnexal masses is carried out attending to imaging methods, fundamentally ultrasonography, and serum tumor markers.

There are different scoring systems to evaluate adnexal masses ultrasonographically. Ultrasound signs of malignant ovarian tumors include multilocular or multiple cysts, thick or irregular septa or walls, poorly defined borders, papillary projections, solid components and echogenic elements (Table 1).

<table>
<thead>
<tr>
<th>Scores</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limits</td>
<td>Defined</td>
<td>Partly poorly defined</td>
<td>Poorly defined</td>
</tr>
<tr>
<td>Borders</td>
<td>Regular</td>
<td>Partly irregular</td>
<td>Mostly irregular</td>
</tr>
<tr>
<td>Echogenicity</td>
<td>Solid echo</td>
<td>High echogenicity</td>
<td>Mixed echogenicity</td>
</tr>
<tr>
<td>Inner walls structure</td>
<td>Smooth and &lt; 3 mm</td>
<td>Irregular and/or &gt;3 mm</td>
<td>Papillaries</td>
</tr>
<tr>
<td>Septa</td>
<td>No</td>
<td>&lt; 3 mm</td>
<td>&gt; 3 mm</td>
</tr>
</tbody>
</table>

Solid echogenicity within the tumor is considered potentially malignant, although a high false-positive rate should be considered in the differential diagnosis of malignant masses. Conventional color and pulsed Doppler have been introduced to improve the diagnostic accuracy of gray-scale morphological ultrasonography, but the results are of limited value.

In spite of technical advances, survival rates of ovarian cancer have not been improved, for what is necessary to continue investigating in new more sensitive and specific techniques to improve early diagnosis of ovarian tumors.
Three-dimensional ultrasound offers two advances over conventional ultrasound, improved spatial orientation in association with surface rendering and objective quantification of an organs volume and blood flow.\textsuperscript{13}

Regarding ovarian tumors, potential advantages of 3D ultrasound would be a more accurate diagnosis of ovarian cancer and the possibility of its detection in early stages. 3D power Doppler angiography (3D-PDA) allows the acquisition of power-Doppler data from an organ or area of tissue as a whole, which may then be displayed providing a means to assess spatial parameters of tissue vascularity (such as a cluster or branching patterns of a vascular network). Through the histogram facility we can investigate tumor neovascularity, calculate vascularity, parameters and assess tumors blood flow in different stages of growth. There are three indices of vascularity to quantificate an organs blood supply applying

\begin{center}
The Role of 3D Ultrasound and 3D Power Doppler Imaging in the Diagnosis and Evaluation of Ovarian Cancer
\end{center}

3D-PDA: Vascularization index, that reflects the ratio of power Doppler information within the total dataset relative to both color and gray-scale information, the flow index, that represents the mean power Doppler signal intensity, and the vascularization flow index, that is a combination of the two.\textsuperscript{14-16}

**NEW PERSPECTIVES**

The potential advantages of 3D ultrasound over conventional ultrasonography have been examined in a number of studies to determine their diagnostic value in women with possible gynecological malignancies. These studies vary greatly in their design and patient populations, and offer extensive and possibly contradictory results.

In a pioneer work, Bonilla-Musoles et al tried to determine whether 3D ultrasound may offer advantages over 2D ultrasound as a screening tool for the evaluation of ovarian lessons. They evaluated 76 women with ovarian masses first detected with conventional ultrasound, basing the 3D sonographic criteria for malignancy in the morphologic scoring system for 2D ultrasound proposed by different authors. They stated that observation of papillary projections, characteristics of cystic walls, and the extent of capsular infiltration was superior with 3D ultrasound in comparison to conventional 2D sonography, as was the calculation of ovarian tumor volume. They also indicated that eventually 3D ultrasound imaging will allow diagnosis of ovarian malignancy at an earlier stage (Figs 1 and 2).\textsuperscript{17}

Hata et al, in a study of 20 ovarian tumors, reported a higher specificity and accuracy, and a lower false-positive rate for 3D ultrasound compared with 2D sonography, suggesting that 3D ultrasonography might be a better means of differentiating between malignant and benign ovarian tumors.\textsuperscript{18} Both works considered similar morphologic criteria for the diagnosis of ovarian malignancy. Other authors, however, point out that the most important variable in predicting malignancy is the presence or absence of solid
elements within the tumor, and find that the use of 3D transvaginal sonography does not significantly improve the 2D transvaginal sonographic morphologic assessment of complex adnexal masses, though it is useful for reinforcing initial diagnostic impressions.\textsuperscript{19-21}

Concerning power Doppler evaluation of complex adnexal masses, Cohen \textit{et al} published a study over 71 women in which despite all malignancies were correctly identified by both 2D and 3D imaging, the specificity was significantly improved with the addition of 3D power Doppler.\textsuperscript{22}

In an analysis of 43 patients with suspected stage I ovarian cancer, Kurjak \textit{et al} show that 3D power Doppler and especially the combined use of 3D sonography and power Doppler imaging significantly improve diagnosis accuracy in preoperative sonographic assessment of suspected ovarian lesions.\textsuperscript{23,24}

Fishman \textit{et al} examining the usefulness of sonography in the detection of early-stage of epithelial ovarian cancer find that specificity significantly improved by the addition of 3D Doppler imaging as a secondary test to determine the location of blood flow, but Guerriero \textit{et al} argued that there is little evidence that 3D Doppler imaging is significantly better than results with 2D gray-scale and color Doppler imaging. Likewise, Testa \textit{et al} deem that the use of 3D quantification of tumor vascularity yields a diagnostic accuracy, that is, similar to that of subjective evaluation of vascularity.\textsuperscript{25-27}

Alcazar \textit{et al}, however, find that the 3D-PDA index seems to improve the accuracy in evaluation of complex vascular masses compared with conventional power Doppler index.\textsuperscript{28}

CONCLUSIONS

Three-dimensional sonography examination contributes to carry out a volumetric reconstruction of the examined objects and allows an objective quantification of blood flow. Some studies suggest that it might be a better means in the evaluation of complex adnexal masses. Therefore, further studies are necessary to demonstrate the improved sensitivity and specificity compared to conventional 2D ultrasound (Fig. 3).

REFERENCES
• Alcazar JL, Jurado M. Prospective evaluation of a logistic model based on sonographic morphologic and color Doppler findings developed to predict adnexal malignancy. J Ultrasound Med 1999;18: 837-42.


• Kurjack A, Kupesic S, Sparac V, Prka M, Bekavac I. The detection of stage I ovarian cancer by three-dimensional sonography and power Doppler. Gynecol Oncol 2003; 90(2):258-64.


Ovarian Cancer Screening: the Role and Drawbacks of Ultrasonography and Feasibility in Low Resource Settings

Chukwuemeka Anthony Iyoke1,*, Osaheni LuckyLawani2, George Onyemaechi Ugwu1, Euzebus Chinonye Ezugwu1, Leonard Ogbonna Ajah2, Robinson Chukwudi Onoh2

1Department of Obstetrics and Gynaecology, University of Nigeria Teaching Hospital, Ituku-Ozalla, Enugu, Nigeria 2Department of Obstetrics and Gynaecology, Federal Teaching Hospital, Abakaliki, Nigeria *Corresponding author: caiyoke@yahoo.co.uk

Received August 30, 2014; Revised January 20, 2015; Accepted January 26, 2015

Abstract Context: Although there have been reports of increasing incidence of ovarian cancer in developing countries, no developing country has been involved in current trials of ovarian cancer screening. Aim: To review the evolution of the role and drawbacks of ultrasonography in ovarian cancer screening and the feasibility of implementing current potential screening strategies in low resource settings. Methods: An electronic literature search for all articles written in English language on ovarian cancer screening from 1960-2013. Information from appropriate articles were collated and analysed for content. Results: Ultrasound was used as the first-line or second-line test in the most popular multicentre multimodal trials of ovarian cancer screening. It has a high sensitivity but a low specificity. The low specificity of ultrasound screening necessitates the use of further measures to aid the triaging of ultrasound positive cases, which add to the overall cost of screening. There is yet scant evidence of the cost effectiveness of multimodal screening for ovarian cancer. Current potential strategies for ultrasound-based screening for ovarian cancer demand the training and employment of large numbers of highly skilled personnel as well as the acquisition of high resolution scanners and technology for biochemical assay of tumour markers. Conclusion: Transvaginal ultrasonography has evolved into a potential tool for ovarian cancer screening and ovarian cancer screening strategies based on CA125 assays and ultrasonography would demand substantial resources. If and when reduction in mortality and cost-effectiveness of this approach to screening are proven, it may not be feasible in developing countries.

Keywords: transvaginal ultrasound, ovarian cancer, screening, CA125, low-resource countries


1. Introduction
Recent trials of ovarian cancer screening have shown that current modalities for screening increase the detection of early stage ovarian cancer [1]. Five-year survival for early stage cancer is
significantly higher than for late disease [1]. This survival advantage for patients diagnosed with early stage ovarian cancer suggests that screening programs that detect early stage disease might have an impact on disease mortality [2]. Evidence from screening women with family history of ovarian cancer or with confirmed inherited high-risk genes such as BRCA 1, 2 showed that 4-monthly CA125 followed by ultrasound for positive cases increased the rate of complete cytoreductive surgery to 92% compared to 62% for annual screens [3,4]. However, till date, the ability of screening to decrease overall mortality from ovarian cancer in populations at risk is not yet established [1,2]. The United States Preventive Services Task Force (USPSTF) “recommends against screening for ovarian cancer in asymptomatic women, except those with known genetic mutations that increase their risk for ovarian cancer (for example, BRCA mutations)” [5].

In the last three decades, the potential usefulness, acceptability and limitations of ultrasound individually or as part of a multimodal approach to ovarian cancer screening have been well documented [6-10]. A challenge arising from the limitations of ultrasound is how to minimize the false positive tests associated with ultrasound screening. The low specificity of ultrasound screening makes it unsuitable as a sole screening modality and necessitates the application of further measures such as clinical assessment, biochemical assay of tumour markers, morphologic indices, logistic regression models, risk of malignancy indices to aid the triaging of ultrasound positive cases. The aim is to further identify all benign lesions among all cases that initially tested positive to ultrasound screening. Such benign lesions can then be safely managed conservatively by serial scans.

For ultrasound screen-positive benign lesions involving simple cysts, further management is well defined because the natural history of small simple ovarian cysts is, perhaps, conclusively determined: they either disappear or persist and they do not transform to cancer [11,12]. Conservative management of simple cysts is therefore the rule. When such lesions involve benign septated (complex) cysts, further management has been shrouded in uncertainty because the natural history of such lesions is less clear: disappearance, persistence and transformation to cancer have all been described. Whereas in the Prostate, Lung, Colorectal and Ovarian cancer (PLCO) trial, no increased risk of cancer was found compared to women without cysts, analysis of United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) data reached a similar conclusion but suggested that septated (multilocular) cysts did transform to mostly borderline and few early type I ovarian cancer [1,13]. A recent study has also shown transformation of conservatively-managed septated cysts to ovarian cancer through increasing complexity in morphological features [14]. The link between benign complex cysts and ovarian cancer therefore remains controversial today as it was two decades ago [15].

We reviewed literature on the evolution of ultrasonography as a possible screening tool for ovarian cancer and the management of ultrasound positive screening tests. We highlight in particular the dilemmas that may confront ultrasound practitioners and gynaecological oncologists involved in the selection and treatment of women that are triaged to conservative management following
positive ultrasound screening tests. We explored the feasibility of mounting ovarian cancer screening based on CA125 and ultrasonography in developing countries, especially in Sub Saharan Africa.

2. Search Methodology
The information contained in this review were obtained through electronic literature search conducted in major data bases including PubMed, Medline, EMBASE, Scopus, CINHAL, Cochrane database and central register of controlled trials using the following search terms individually and in combination: ovarian cancer, simple ovarian cysts, complex ovarian cysts, screening trial, ultrasonography, transvaginal ultrasound, multimodal, PLCCO trial, cost effectiveness of screening, UKFOCCS, UKCTOCS. All relevant peer-reviewed English language articles and publications were identified, retrieved and reviewed. We also obtained further articles by reviewing the bibliographies of the relevant published articles. Figure 1 shows a flow chart of the results of literature search.

3. History of Ovarian Cancer Screening
The history of screening for ovarian cancer can be broken into three phases based on the major focus of efforts at screening. The first phase would be the period from the 1950 to 1980 during which efforts at screening were made, at best, at informal, individualized and opportunistic level. Methods used
included digital pelvic examination and cul-de-sac aspiration [16,17]. These methods had low sensitivity and specificity and were abandoned due either to complications arising from them and/or poor patient acceptability and compliance [18]. The introduction of ultrasound into medicine during this period resulted in transabdominal ultrasound being used to characterize abdominal and pelvic masses including ovarian tumours in symptomatic women [19, 20].

The second period was the period between 1980 and 1990 during which formalised intense efforts at discovering and establishing appropriate modalities for screening for ovarian cancer began all over the world. During this period real time ultrasonography evolved with the introduction of the transvaginal probe. Similarly the antigen CA125 was discovered and its role as a biomarker identified [21]. In 1985, the first randomized clinical trial of ovarian cancer screening commenced enrolment in Shizouka district of Japan and the trial ran till 2002. This was a multimodal screening using pelvic examination and ultrasonography as a primary modality and CA125 as a secondary modality [22]. In 1989, a pilot randomized controlled trial of multimodal screening utilizing CA125 as primary modality and ultrasonography as secondary modality commenced in the United Kingdom [23]. A number of biomarkers other than CA125 were also tried as possible screening tests for ovarian cancer [24].

The third period from 1990 till date represent the period when real efforts were made at undertaking randomized controlled studies to determine the effect of ovarian cancer screening on mortality from ovarian cancer in at-risk populations. Also intense activity went on in developing new biomarkers and in introducing the use of proteomics to identify antigen profiles related to ovarian cancer. In order to address the inadequacies in the use of absolute values of CA125 for screening, measurement of the rate of rise of the serum levels of the protein was devised. This measurement, called Risk of Ovarian cancer algorithm has been shown to be more specific for ovarian cancer than absolute point measurements since serum levels of CA125 remain steady or decline over time in benign ovarian conditions [25,26]. To further increase the sensitivity and specificity of serum screening, a number of tumour marker panels were tried. Combinations of tumour markers such as CA125, Human Epididymis protein4, Transthyrenin, etc have been tried. To date, no tumour marker panel has been shown to be superior to CA125 followed by transvaginal ultrasound scan [24]. Several novel screening methods have been proposed and a number of these have been tested. Assay of biomarkers in urine of postmenopausal women is said to hold some attraction because of its simplicity and non-invasiveness [27].

Two large randomized controlled trials of ovarian cancer screening were commenced. The PLCO trial began recruitment in 10 centres in the United States in 1993 and final results were reported in June 2011 [28,29]. The trial has determined that ovarian cancer screening did not reduce ovarian cancer mortality in the population, but genuine concerns have already been raised about the methodological approaches that led to this conclusion [30]. A larger trial powered to determine the effect of screening on mortality, the UKCTOCS, commenced recruitment in 13 centres in the UK in 2001 and concluded screening in December 2011 [31]. Unlike the PLCO trial, the UKCTOCS would also determine the relative efficacy of ultrasonography compared to multimodal screening involving CA125 as primary modality followed by ultrasonography where CA125 is abnormal. The final results of the UKCTOCS are expected in 2015.
3.1. The Evolution of Transvaginal Ultrasonography as a Screening Tool for Ovarian Cancer

Table 1 shows a selection of studies that underlined the evolution of ultrasonography as a potential tool for ovarian cancer screening. In addition to the studies listed in the table, other studies had also shown that the cost of screening with ultrasonography compared well with other methods. A major area of concern with transvaginal ultrasound screening remained the significant level of false positive tests which could result in many unnecessary interventions and surgeries. The vital place of ultrasound scan in screening for ovarian cancer was, perhaps, further underscored by the fact that assay of CA125 detects only 50-60% of early ovarian cancers [40]. Thus, although ultrasound scan could give rise to many false positive results, its capacity to detect adnexal lesions even when CA125 assay was normal made ultrasonography an important complement to CA125 for ovarian cancer screening.

<table>
<thead>
<tr>
<th>Year &amp; country of study</th>
<th>Authors</th>
<th>Title of study</th>
<th>Key findings (reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1982, UK</td>
<td>Campbell S, Goswamy R, Goessens I, Whitehead M</td>
<td>Real time ultrasonography for determination of ovarian morphology and volume. The Lancet, 1982: 425-426</td>
<td>Demonstrated the correlation between ovarian volume measurements by ultrasound and measurements of the ovary during surgery. The study indicated the possible use of real time ultrasonography as an early screening test for ovarian cancer in asymptomatic women [32].</td>
</tr>
<tr>
<td>1988, UK</td>
<td>Jacobs I, Stabile I, Bridges J</td>
<td>Multimodal screening for ovarian cancer. The Lancet, 1988: 268-72</td>
<td>Demonstrated that CA125 and Ultrasonography each test lacked the specificity to screen for ovarian cancer individually but that CA125 and ultrasonography achieved acceptable specificity together [35].</td>
</tr>
<tr>
<td>1993, USA</td>
<td>van Nagell Jr JR, DePriest PD, Gallion HH, Pavlik EJ</td>
<td>Ovarian Cancer Screening Cancer. 1993; 71: 1523-8</td>
<td></td>
</tr>
<tr>
<td>1995, USA</td>
<td>van Nagell Jr JR, Gallion HH, Pavlik EJ, DePriest PD</td>
<td>Ovarian Cancer Screening. Cancer 1995; 76:2086-91.</td>
<td>high resolution transvaginal ultrasonography was univasive, painless, well accepted by women and was able to determine precise ovarian dimensions that correlated well with measurements of the ovary obtained during surgery [38,39].</td>
</tr>
<tr>
<td>1997, USA</td>
<td>DePriest PD, Gallion HH, Pavlik EJ</td>
<td>Transvaginal sonography as a screening method for the detection of early ovarian cancer. Gynecologic Oncology, 1997; 65: 408-414</td>
<td>Transvaginal sonography reduced stage at detection and case-specific mortality and recommended a multi-institutional ovarian cancer screening trial to determine effect on mortality in the population [37].</td>
</tr>
</tbody>
</table>
4. Management of Positive Ultrasound Screening Tests

A few challenges confront the gynaecologist following a positive ultrasound screening for ovarian cancer. The first challenge is the necessity to avoid any delay in intervention that may lead to disease progression; the second is to avoid unnecessary surgical interventions in those who may have had false positive screening tests and the third and the least recognized is the challenge posed by the unpredictability of the biologic behaviour of cases that are triaged to conservative management. As a consequence of the third challenge, it has been observed that a “proportion of women and clinicians will opt for surgery once a complex adnexal lesion is detected even if it is likely to be benign” [31].

4.1. Triaging Ultrasound Positive Results

Triaging is important in order to refer those with a high likelihood of cancer to Oncology centres early enough in order to maximize the benefit of screening and also to avoid unnecessary surgeries in those with false positive results. Avoiding unnecessary surgical interventions requires taking extra steps to further identify those who are most likely to have benign lesions among the screen positive tests. This could involve repeat ultrasound scan by an expert ultrasound practitioner, clinical examination by a gynaecologist as well as biochemical assays of CA 125. In addition to these, several procedures are available as adjuncts to aid the triaging of adnexal masses (screen positive cases) to either surgical intervention or conservative management. These include the use of morphologic indices, risk of malignancy indices and mathematical models etc. Although many of these were described for symptomatic ovarian masses, they can also be used in screen positive cases and therefore merit elaboration.

4.1.1. Morphologic Indices

These techniques include the use of scoring systems based on morphological features noted on ultrasound images to distinguish between benign and malignant ovarian lesions. Sonographic morphological features of ovarian cysts such as the thickness of cyst wall, presence of papillary growths on cyst wall, presence of solid components within the cyst, presence and number of loculations, sonolucency of cyst fluid and presence of shadowing have been incorporated into scoring systems. There are many scoring systems now but the commonest include the Granberg score, Sassone score, the Kentucky score, Lerner’s score, Ferrazzi’s score, Alcazar score [41-47]. The Granberg score is a single index scoring system based on locularity of the adnexal cyst with unilocular cyst given a score of zero, unilocular solid score of 1, multilocular cysts score of 2 and multilocular solid and pure solid cysts given score of 3 and 4 respectively [41]. The Granberg score has a sensitivity and specificity of 87% and 49% respectively for a score of 2 (multilocular cysts) for a positive predictive value of 31% [41]. The Granberg score is one of the earliest morphologic scoring indices and has been largely superseded by later scoring indices. The Sassone score utilizes features including inner wall structure, wall thickness, septal thickness and echogenicity scored on a scale of 1 to a maximum of 5 where applicable [44]. For a cut off of score of 9, it has a sensitivity, specificity and positive predictive value of 74%, 65% and 36 respectively. The Kentucky score uses 3 parameters namely cystic wall structure, ovarian volume, and septal structure [43]. For a cut off score of 5 it has a sensitivity, specificity and positive predictive value of 88%, 40% and 28% respectively. The Alcazar score includes features from Doppler studies such as velocimetry and blood flow location [47]. The efficacy of all these scoring systems when used alone is hampered by an overlap between the appearances of benign and malignant adnexal masses [48].
4.1.2. Risk of Malignancy Indices

To increase the sensitivity and specificity of morphological scoring systems, some scientists have combined ultrasound features with other parameters such as clinical features or assay of biomarkers to create risk scoring indices. The risk of malignancy index devised by Jacobs and co-workers, for instance, combines scores based on menopausal status, ultrasound features and CA125 level [49]. It had a sensitivity of 85% and specificity of 97% [49]. Since the introduction of this index, several other risk-of-malignancy indices have been introduced, each new index seeking to improve on diagnostic accuracy by improving on the specificity or sensitivity of previous ones [50,51,52]. While the original risk of malignancy index by Jacobs and co-workers is referred to as RMI 1, other RMIs have followed the RMI 1 thus: RMI 2 by Tingulstad and colleagues 48, RMI 3 also by Tingulstad and colleagues [51] and RMI 4 by Yamamoto and co-workers [52]. A recent comparison of the performances of RMIs 1-4 showed that there was no statistically significant difference in their ability to discriminate between malignant and non-malignant adnexal masses [53]. The sheer multiplicity of indices underlies the inadequacy of each RMI and this has limited the usefulness of these aids for the triaging of ovarian lesions diagnosed during screening.

4.1.3. Mathematical Models

4.1.3.1. Logistic Regression Models

In order to further improve clinical decision making following a positive screening test, logistic regression models using socio-demographic and clinical features were introduced to assist in discriminating between malignant and benign ovarian lesions prior to surgery. Several authors have introduced or validated previously devised logistic regression equations and found them to demonstrate a high sensitivity, specificity and positive predictive value [47,54,55,56]. Prospective validation has been possible with the IOTA logistic regression equation [53]. The logistic regression model proposed by Tailor and co-workers had a sensitivity of 93.3% and specificity of 90.4% [56], while the IOATA logistic regression had a sensitivity of 93.0% and a specificity of 76% [54]. Alcazar and colleagues introduced Doppler flow characteristics and reported a sensitivity of 84.6% and specificity of 100% [47].

4.1.3.2. Computer-based mathematical techniques

In addition to morphological scores, risk of malignancy indices and logistic regression equations, other techniques such as self-teaching computer based neural networks [57] and the use of least support square vector machines are other mathematical devices that have been introduced to the distinguish between benign and malignant adnexal tumours prior to surgery [58]. Timmermann and co-workers obtained a sensitivity of 95.9% and specificity of 93.5 for artificial neural networks in discriminating between malignant and benign ovarian masses [57]. These techniques are advanced statistical applications that cannot be easily understood by most clinicians and this limits their usefulness for routine clinical practice.

5. Predicting the Biologic Behaviour of Triaged Benign Cysts

Appreciation of the precise biologic behaviour of benign ovarian cysts is important for conservative management. Overall, the biologic behaviour and outcomes of conservative management have tended to differ between benign simple cysts and benign complex cysts.

5.1. Simple Ovarian Cysts

Prior to the advent of transvaginal sonography, studies based on transabdominal ultrasound scan showed that small anechoic ovarian cysts were seldom malignant in elderly women. In a
retrospective study of 152 symptomatic Swedish women aged 50 years or more presenting in the Gynaecology clinic, in whom cystic lesions without solid parts had been diagnosed, Andolf and Jørgensen found no malignancies in 58 completely anechoic lesions less than 5 cm and of small lesions less than 5 cm with some echogenicity or septa, they found 1 borderline tumour [59]. In contrast they found 5 malignancies in a group of 32 women who had cysts measuring more than 5 cm with some echogenicity and 8 malignancies among 18 lesions greater than 5 cm with septa [59]. The study excluded those with multicystic lesions without solid parts. The study demonstrated that small unilocular anechoic cysts were hardly malignant. However, since no follow up on these simple cysts was done, no conclusion could be drawn on their biologic behaviour from this study.

With the advent of transvaginal sonography, Sasaki and colleagues conducted a follow up study of 225 pre and postmenopausal women with ovarian cysts less than 6 cm with change in size as the main outcome measure [60]. After 6.25 years, 29 lesions had progressed (13%), 14% had persisted while 73% regressed with 48% regressing within 6 months [60]. Of the 29 the progressed, 9 had surgery and no cancer was found [60]. The other 20 lesions that progressed were not accounted for. The design of the study that sought change in size as main outcome measure clearly limited the conclusions that could be drawn from the study and the inability to explore a majority of the lesions that progressed deprived the study of a window view into the possible relationship of a progressing simple cyst with malignant transformation.

A study to measure the occurrence and natural history of simple ovarian cysts in older women participating in a large randomized trial of ovarian cancer screening, Greenlee and co-workers found that among 15,735 women whose ovaries were visualized, 2,217 had a simple cyst at first scan and that those with one simple cyst had 33% regression after one year and those with two or more cysts had less regression after one year [61]. Only six percent of simple cysts developed complex cysts or solid areas after one year compared to 7% of two simple cysts and 11% of multiple cysts [61]. Interestingly, only 1% of those who had no cysts initially developed cysts with complex or solid parts. Overall the study concluded that the development of malignancy did not differ significantly between those who had simple cysts and those who had no cysts at all at the initial scan after a median follow up of 7 years [61]. Perhaps because of the finding that the development of complex cysts or cysts with solid areas occurred more in those who had simple cysts at the initial scan than in those with no cysts at all, it affirmed the conclusion of previous studies that simple cysts rarely led to cancer but cysts that persist should be followed up [61].

A prospective cohort study that assessed the malignant potential of ovarian inclusion cysts in postmenopausal women aged 50 years or more who were participants in the UKCTOCS found no increase in relative risk of cancer between those with inclusion cysts and those without after a median follow up of 6.13 years [62]. They however found that the risk of ovarian cancer increased in those who had ovaries with both inclusion cysts and simple/complex cysts as opposed to those who had inclusion cysts alone [62].

These two large series support view that simple cysts are probably not premalignant. However, they tend to suggest that those that have simple cysts that persist tend to develop complex cysts more than those who do not have cysts and that those with complex cysts tend to have increased incidence of subsequent malignancy.

5.2. Septated (Complex) Ovarian Cysts

Data on conservatively-managed complex ovarian cysts with benign ultrasound morphology are scanty and their contribution to the development of ovarian cancer is still not clear. This partly explains why surgical rates are high in trials of ultrasound screening for ovarian cancer. Unlike
simple cysts that generally tend to regress, a recent study of pre and postmenopausal women showed that 62% of complex cysts persisted over a mean period of 77 months [63].

In order to determine whether asymptomatic ovarian abnormalities detected on ultrasonography in postmenopausal women are precursors to ovarian cancer, Hartge and co-workers studied complex cysts defined as having septa, irregular thick wall or solid component using correlation analysis and logistic regression [64]. They used known risk factors for ovarian cancer such as old age at examination, age at menopause, family and personal history of breast or ovarian cancer and history of infertility as predictor variables [64]. The study concluded that complex ovarian cysts did not appear to be immediate precursors of ovarian cancer because risk factors for ovarian cancer such as a family history of ovarian cancer were not associated with complex cysts in their series [64].

In a study to determine the risk of malignancy in septated cystic ovarian tumours by Saunders and colleagues, 1319 women with septated cystic tumours were placed on long term surveillance for ovarian malignancy [63]. Of 2288 tumours, 1114 regressed spontaneously while 1756 persisted [63]. Patients were followed for 4 - 252 months with a mean of 77 months and only one patient developed epithelial ovarian cancer and the others were free of cancer after 7642 follow-up years [63]. The study concluded that septated ovarian cysts had very low risk of malignancy [63]. The fact that only one case of cancer developed among 1756 tumours after a mean follow up of 77 months is an interesting finding that suggests that such cysts pose little or no risk of malignancy [63]. However, the study included both premenopausal-who have no increased risk of ovarian cancer-and postmenopausal women. The study also did not describe the changes, if any, in the features of the cysts with time and so no information on transformation of such cysts other than into cancer was provided. A mean follow up of 77 months (71/2 years) would be enough time for changes to be noted in the morphological features of the cysts.

On their part, Sharma and co-workers determined the risk of malignancy in asymptomatic postmenopausal women with ultrasound detected ovarian cysts detected during the prevalence screen of the UKCTOCS trial [62]. They found that of 1095 women with septated cysts without solid elements, four developed primary ovarian cancer and all 4 were initially managed conservatively and all had an increase in size or changes in features of the cysts prior to diagnosis of cancer [62]. The change in morphology prior to diagnosis of cancer could suggest some form of malignant transformation of previously benign cysts [62].


6.1 Cost Effectiveness of Ovarian Cancer Screening

Few studies have directly addressed the cost effectiveness of ovarian cancer screening [65,66,67,68]. A cost-effectiveness analysis is defined by the United Kingdom's National Institute for Health and Clinical Excellence (NICE) as an economic study design in which the consequences of different interventions are measured using a single outcome, usually in "natural" units such as life-years gained or cases detected [65]. Alternative interventions are then compared in terms of cost per unit of effectiveness. For ovarian cancer, it would mean the cost of detecting one case of ovarian cancer. Three categories of costs are considered: (i) cost associated with the screening tests themselves, (ii) costs associated with evaluation of positive screens, and (iii) cancer treatment costs [66]. Using stochastic modelling, Urban and colleagues have estimated that using a multimodal strategy with CA125 assay followed by ultrasound for positive cases would cost US $51,000 per year of life saved [67]. Generally, estimates range 100,000 – 250,000 (USD) per life year saved, although it has been suggested that the cost per year of life saved through screening must be <150,000 US dollars to be cost-effective, putting into consideration the cost of interventions,
unnecessary surgeries and complications of surgery. However, cost-effectiveness might vary according to different medical environments in different nations.

6.2. Feasibility in Low Resource Settings of Current Screening Strategies under Trial

Contrary to previous beliefs, there are indications that the prevalence of ovarian cancer may be increasing in developing countries as a shift to sedentary lifestyles and western diets and social habits spreads [69,70,71]. There is therefore the need for a more than cursory attention to be paid to this disease in developing countries. Despite this development, no trial of ovarian cancer screening has been reported from any developing country.

The implications of current ovarian cancer screening protocols for developing countries are multifold. First, the sheer capital outlay required for large trials is beyond the capacity of most developing economies in terms of funds and personnel required. The UKCTOCS trial needed hundreds of millions of pounds and thousands of highly-skilled health personnel including sonographers, gynaecologists and secretarial staff. Cost-effectiveness studies on ovarian cancer screening appear to have been based on procedural costs alone, in line with the NICE definition. For low-income countries a wider perspective of cost must be applied. Unlike in developing countries, the cost of acquisition of equipment and training of personnel, both of which are not on the ground in most low-resource countries, must be factored in. It might therefore not be possible, nor cost-effective for any developing country in Sub-Saharan Africa to acquire and expend such resources on such a rare disease as ovarian cancer.

Since neither ultrasound nor assay of CA125 possesses sufficient specificity individually to be used alone for screening, multimodal approach to ovarian cancer screening has come to stay. Ultrasound screening is an expensive endeavour given the cost of modern high resolution machines required for precise ovarian morphological characterization. Besides, the high level of ultrasound skill required for transvaginal scanning of postmenopausal women may not be widely available in many developing countries. Assay of CA125 also requires high tech laboratories with appropriately trained personnel. If CA125 assay was sensitive and specific enough on its own, it might still be too expensive for many developing country economies. The necessity for further tests and scans after the initial positive tests increases the cost of screening.

7. Conclusion

Transvaginal ultrasonography remains a potential tool for ovarian cancer screening. It has a high sensitivity. However, its low specificity suggests that it is best used as an adjunct to other screening methods. Confronted with the challenges of high false positive rates, further clinical assessment and biochemical tests are mandatory following positive ultrasound test both to achieve a high specificity and to ensure appropriate triaging and management of positive results. These extra measures add to the cost of screening. Globally very few studies have evaluated the cost effectiveness of ovarian cancer screening, and there is no clear agreement that current multimodal strategies are cost effective since no mortality benefit has been demonstrated. For developing countries, the technological and human resources needed for current potential screening strategies could make screening for ovarian cancer unattainable.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this article.
UK Familial Ovarian Cancer Screening Study (UK FOCSS Phase 2).


[41] Granberg S, Wikland M, Janson I. Macroscopic characterisation of ovarian tumours and the relation to histological diagnosis: criteria to be used for ultrasound evaluation. Gynecologic Oncology, 35: 139-44.


Ovarian Cancer Screening With Annual Transvaginal Sonography

Findings of 25,000 Women Screened

BACKGROUND. Ovarian cancer has the highest mortality rate of all gynecologic malignancies, and most women present with advanced-stage disease. The current investigation was performed to determine the efficacy of annual transvaginal sonography (TVS) as a screening method for ovarian cancer.

METHODS. Annual TVS screening was performed on 25,327 women from 1987 to 2005. Asymptomatic women aged ≥50 years and women aged ≥25 years who had a family history of ovarian cancer were eligible for participation in this trial.

RESULTS. Among 364 patients (1.4%) with a persisting ovarian tumor on TVS who underwent exploratory laparoscopy or laparotomy with tumor removal, 35 primary invasive ovarian cancers, 9 serous ovarian tumors of low malignant potential, and 7 cancers metastatic to the ovary were detected. Stage distribution was as follows: 28 patients had stage I disease, 8 patients had stage II disease, and 8 patients had stage III disease. Four patients died of disease, 2 patients died of other causes, and 38 patients were alive and well from 0.5 years to 15.8 years after diagnosis (mean, 5.3 years). Nine women developed ovarian cancer within 12 months of a negative screen (false-negative results), and 3 of these patients died of disease. TVS screening had a sensitivity of 85.0%, specificity of 98.7%, positive predictive value of 14.01%, and negative predictive value of 99.9%. After 107,276 screening years, there have been 7 ovarian cancer deaths in the annually screened population and 3 ovarian cancer deaths among women who were noncompliant. Excluding patients with nonepithelial or borderline ovarian malignancies, the survival of patients with ovarian cancer in the annually screened population was 89.9% ± 10.1% at 2 years and 77.2% ± 22.8% at 5 years. CONCLUSIONS. TVS screening, when it was performed annually, was associated with a decrease in disease stage at detection and with case-specific ovarian cancer mortality, but it was not effective in detecting ovarian cancers in women who had normal ovarian volume. Cancer 2007;109:1887–96. © 2007 American Cancer Society.

KEYWORDS: gynecologic malignancies, laparoscopy, morphology index, ovarian volume, predictive value, screening frequency.
Despite advances in radical surgery, postoperative care, and chemotherapy, ovarian cancer remains the fourth leading cause of cancer mortality among women in the United States.¹ This year, over 16,000 deaths from ovarian cancer will be reported in the United States alone. Early-stage ovarian cancer produces few specific symptoms, and pelvic examination is notably inaccurate in detecting subtle changes in ovarian size and morphology, particularly in postmenopausal women.² Consequently, most patients continue to present with advanced-stage disease, for which the prognosis is poor. Early-stage ovarian cancer, however, is highly curable when it is treated by conventional therapy.³,⁴ Therefore, screening asymptomatic, high-risk women has been proposed as a means to detect ovarian cancer at an earlier and more curable stage.⁵⁻¹³

In 1987, the University of Kentucky Ovarian Cancer Screening Project was initiated to assess the efficacy of annual transvaginal sonography (TVS) as a screening method for ovarian cancer. Since then, free screening has been provided to >25,000 women. The screening algorithm used has remained the same, except that, now, women with persisting, uni-locular, cystic ovarian tumors that measure <5 cm in greatest dimension are followed at 6-month intervals with ultrasound instead of undergoing laparoscopic tumor removal. The current report summarizes the data from the trial.

MATERIALS AND METHODS

Patients

Patients who enrolled in the University of Kentucky Ovarian Cancer Screening Project from January 1987 to May 2005 were evaluated. Eligibility criteria included 1) all asymptomatic women aged ≥50 years and 2) asymptomatic women aged ≥25 years with a documented family history of ovarian cancer in at least 1 primary or secondary relative. Genetic testing was not performed routinely as part of this trial. All study participants completed a questionnaire that included past medical history, surgical history, menopausal status, hormonal use, and family history of cancer. Menopause was defined as the absence of menses for 12 months. Any woman with a known ovarian tumor or a personal history of ovarian cancer was excluded from this investigation.

After informed consent was obtained, each patient underwent screening according to the algorithm illustrated in Figure 1. TVS was performed initially with Aloka 620 and Aloka 680 ultrasound units (Aloka, Tokyo, Japan) with a 5-MHz vaginal probe, as described
Since 2000, TVS has been performed using General Electric (Milwaukee, Wis) Logiq 400 units with a 5-mHz vaginal probe. Doppler flow and 3-dimensional sonography were performed in selected patients using a General Electric Voluson 730 ProV unit with a 5- to 9-mHz vaginal probe. All sonographic images were reviewed by at least 1 of the authors. At each screen, both ovaries were measured in 3 dimensions. Ovarian volume was calculated by using the prolate ellipsoid formula (length x width x height x 0.523). All screening information was entered into a Medlog database on a local network.

Criteria for abnormality included an ovarian volume >20 cm$^3$ for premenopausal women and >10 cm$^3$ for postmenopausal women. These values were used because they were >2 standard deviations (SD) above the mean volume of normal ovaries in premenopausal and postmenopausal women. In addition, any cystic ovarian tumor with a solid or papillary projection into its lumen was considered abnormal. Women who had a normal screen were scheduled to return in 12 months for a repeat screen. Women who had an abnormal screen underwent a repeat sonogram in 4 to 6 weeks. Women who had an abnormal second screen had a serum CA-125 determination, tumor morphology indexing, Doppler flow sonography, and (more recently) serum proteomic analysis. Morphology indexing was performed according to the classification of Ueland and colleagues. Each tumor was given a score from 1 to 10 according to increasing morphologic complexity and volume (Fig. 2). Women who had unilocular cystic ovarian tumors that measured <5 cm in greatest dimension and a normal serum CA-125 were followed with repeat sonography at 6-month intervals. Women who had persisting, complex ovarian tumors or women who had a cystic ovarian tumor and an elevated serum CA-125 level were advised to undergo surgical removal of the tumor. During the past 10 years of this trial, every effort was made to perform laparoscopic tumor removal as the initial step in the operative evaluation of patients with persisting ovarian tumors detected at screening.

At the time of laparoscopy, ovarian tumors were placed in an endoscopic bag intra-abdominally and removed through a midline subumbilical incision. Patients with ovarian cancer on frozen section or patients with obvious metastatic disease at laparoscopy underwent immediate exploratory laparotomy and staging. Tumors were classified histologically according to the World Health Organization (WHO) system and were staged according to the International Federation of Gynecology and Obstetrics (FIGO) system. After surgery, patients were treated according to the cell type, histologic differentiation, and stage of each tumor, usually with a 6-month course of combination chemotherapy. Patients with ovarian cancer were followed at monthly intervals during treatment, every 3 months for 2 years, and every 6 months thereafter. Follow-up data on all patients...
were coordinated with the American Cancer Society and the Kentucky State Department of Vital Statistics. Three hundred eighty patients with ovarian cancer who were entered into the University of Kentucky Tumor Registry from 1987 to 2005 and who did not receive screening served as a historic control group for this investigation.

**Statistical Methods**

Proportions were compared by using chi-square statistics or Fisher exact tests. Means were compared by using 2-sample t statistics. Statistical significance was determined at the .05 level. Patient survival was estimated using the Kaplan-Meier method.

**RESULTS**

There were 25,327 women who enrolled in the study from January 1987 to May 2005, and a family history of ovarian cancer was documented in 5868 of those women (23.2%). The clinical characteristics of the patients screened are illustrated in Table 1. The mean age of these patients was 56 years (SD, 10.5 years; range, 25–92 years). The mean height was 162.56 cm (SD, 6.6 cm; range, 127–195.58 cm), and the mean weight was 72.21 kg (SD, 15.9 kg; range, 36–166.9 kg). The mean parity was 2.4 (SD, 1.4; range, 0–17), and 3705 women (14.6%) were nulliparous. Women enrolled in the study underwent a total of 120,569 scans (mean, 4.8 scans per participant). One or both ovaries were visualized in 101,299 scans (84%). Sonographically undetectable ovaries were considered normal for the purposes of this investigation.

Three hundred sixty-four women (1.4%) with a persisting ovarian tumor on TVS underwent surgery. Histologic diagnoses of the 364 ovarian tumors removed are presented in Table 2. The most common diagnosis was ovarian serous cystadenoma followed by primary ovarian cancer and endometrioma. Forty-four women had primary ovarian cancer, including 39 epithelial neoplasms and 5 ovarian stromal neo-plasms. Patients who had a positive family history of ovarian cancer did not have a statistically higher frequency of ovarian carcinoma or benign ovarian tumors than patients without this history. All ovarian malignancies except 1 had solid components or papillary projections from the tumor wall. One ovarian carcinoma was predominantly cystic, but it had an abnormally persisting ovarian tumor on TVS underwent surgery.

**TABLE 1**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Range</th>
<th>No of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>56</td>
<td>25–92</td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td>2.4</td>
<td>0–17</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>71.21</td>
<td>36–166.9</td>
<td></td>
</tr>
<tr>
<td>Height, cm</td>
<td>162.56</td>
<td>127–195.58</td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>5868 (23.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>5938 (37.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon cancer</td>
<td>6068 (24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of hormone replacement</td>
<td>5021 (31.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormone replacement on last visit</td>
<td>5307 (21.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>3705 (14.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 2**

<table>
<thead>
<tr>
<th>Finding</th>
<th>No of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary ovarian cancer</td>
<td>44</td>
</tr>
<tr>
<td>Nonovarian cancer</td>
<td>7</td>
</tr>
<tr>
<td>Appendix</td>
<td>3</td>
</tr>
<tr>
<td>Primary peritoneum</td>
<td>2</td>
</tr>
<tr>
<td>Breast</td>
<td>1</td>
</tr>
<tr>
<td>Endometrium</td>
<td>1</td>
</tr>
<tr>
<td>Serous cystadenoma</td>
<td>153</td>
</tr>
<tr>
<td>Endometrioma</td>
<td>30</td>
</tr>
<tr>
<td>Mucinous cystadenoma</td>
<td>19</td>
</tr>
<tr>
<td>Cystic teratoma</td>
<td>18</td>
</tr>
<tr>
<td>Fibroma/thecoma/Brenner tumor</td>
<td>25</td>
</tr>
<tr>
<td>Leiomyoma</td>
<td>4</td>
</tr>
<tr>
<td>Hydrosalpinx/paratubal cyst</td>
<td>25</td>
</tr>
<tr>
<td>Other</td>
<td>39</td>
</tr>
</tbody>
</table>
thickened wall. Morphology index (MI) scores of the tumors removed varied from 0 to 10. The mean MI value for benign tumors was 3.5 (SD, 2.3; range, 0–10) compared with a mean MI value of 6 (SD, 1.9; range, 3–10) for ovarian malignancies (P < .001). One hundred fifty-three tumors were unilocular without wall abnormalities, and none were malignant.

Clinical and pathologic findings in the 44 patients who had primary ovarian cancer detected by annual screening are presented in Table 3. Stage distribution of these patients was as follows: 28 patients had stage I disease, 7 patients had stage II disease, and 8 patients had stage III disease. Nine patients had serous ovarian tumors of borderline malignancy. Five patients with stage I ovarian metastasis from breast carcinoma who died of disease 7.9 years after ovarian tumor removal, and 1 patient with endometrial cancer and spread to the ovary is alive and well 4.4 years after surgery. To date, there have been no cases of operative mortality in patients who underwent surgery as part of this trial.

**TABLE 3.**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at Dx, y</th>
<th>Family history</th>
<th>No. of screens</th>
<th>Physical examination</th>
<th>TVS finding</th>
<th>TVS volume cm³</th>
<th>TVS MI</th>
<th>CA125, U/ml</th>
<th>Histology</th>
<th>Tumor stage</th>
<th>Treatment</th>
<th>Status</th>
<th>Follow-up, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72</td>
<td>Yes</td>
<td>3</td>
<td>Normal</td>
<td>Complex mass</td>
<td>189</td>
<td>5</td>
<td>7</td>
<td>Serous cell tumor grade 2</td>
<td>IA</td>
<td>S and C</td>
<td>NED</td>
<td>15.8</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>No</td>
<td>1</td>
<td>Normal</td>
<td>Complex mass</td>
<td>19</td>
<td>8</td>
<td>14</td>
<td>Adenocarcinoma grade 3</td>
<td>IA</td>
<td>S and C</td>
<td>NED</td>
<td>15.2</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>Yes</td>
<td>2</td>
<td>Palpable</td>
<td>Cystic mass</td>
<td>27</td>
<td>3</td>
<td>14</td>
<td>Serous cystadenocarcinoma grade 3</td>
<td>IA</td>
<td>S and C</td>
<td>NED</td>
<td>12.3</td>
</tr>
<tr>
<td>4</td>
<td>36</td>
<td>No</td>
<td>1</td>
<td>Normal</td>
<td>Complex mass</td>
<td>32</td>
<td>5</td>
<td>3</td>
<td>Endometrioid carcinoma grade 1</td>
<td>IA</td>
<td>S and C</td>
<td>NED</td>
<td>12.3</td>
</tr>
<tr>
<td>5</td>
<td>55</td>
<td>No</td>
<td>1</td>
<td>Normal</td>
<td>Complex mass</td>
<td>15</td>
<td>6</td>
<td>6</td>
<td>Serous cell tumor grade 2</td>
<td>IA</td>
<td>S and C</td>
<td>NED</td>
<td>11.5</td>
</tr>
<tr>
<td>6</td>
<td>58</td>
<td>No</td>
<td>5</td>
<td>Palpable</td>
<td>Complex mass</td>
<td>94</td>
<td>6</td>
<td>6</td>
<td>Serous ovarian tumor of borderline malignancy</td>
<td>IA</td>
<td>S</td>
<td>NED</td>
<td>8.7</td>
</tr>
<tr>
<td>7</td>
<td>66</td>
<td>No</td>
<td>1</td>
<td>Normal</td>
<td>Complex mass</td>
<td>40</td>
<td>6</td>
<td>37</td>
<td>Endometrioid carcinoma grade 2</td>
<td>IA</td>
<td>S</td>
<td>NED</td>
<td>8.8</td>
</tr>
<tr>
<td>8</td>
<td>64</td>
<td>Yes</td>
<td>1</td>
<td>Normal</td>
<td>Complex mass</td>
<td>25</td>
<td>7</td>
<td>13</td>
<td>Serous ovarian tumor of borderline malignancy</td>
<td>IA</td>
<td>S and C</td>
<td>NED</td>
<td>8.8</td>
</tr>
<tr>
<td>9</td>
<td>63</td>
<td>No</td>
<td>1</td>
<td>Normal</td>
<td>Complex mass</td>
<td>223</td>
<td>8</td>
<td>12</td>
<td>Endometrioid adenocarcinoma grade 2</td>
<td>IA</td>
<td>S and C</td>
<td>NED</td>
<td>8.7</td>
</tr>
<tr>
<td>10</td>
<td>65</td>
<td>No</td>
<td>6</td>
<td>Normal</td>
<td>Complex mass</td>
<td>388</td>
<td>9</td>
<td>25</td>
<td>Endometrioid adenocarcinoma grade 2</td>
<td>IA</td>
<td>S and C</td>
<td>NED</td>
<td>8.7</td>
</tr>
<tr>
<td>11</td>
<td>63</td>
<td>No</td>
<td>1</td>
<td>Normal</td>
<td>Complex mass</td>
<td>164</td>
<td>5</td>
<td>6</td>
<td>Endometrioid adenocarcinoma grade 2</td>
<td>IA</td>
<td>S</td>
<td>NED, DGC</td>
<td>8.7</td>
</tr>
<tr>
<td>12</td>
<td>57</td>
<td>No</td>
<td>3</td>
<td>Normal</td>
<td>Complex mass</td>
<td>3</td>
<td>3</td>
<td>10</td>
<td>Granulosa cell tumor grade 3</td>
<td>IA</td>
<td>S and C</td>
<td>NED</td>
<td>8.7</td>
</tr>
<tr>
<td>13</td>
<td>58</td>
<td>No</td>
<td>10</td>
<td>Normal</td>
<td>Complex mass</td>
<td>35</td>
<td>5</td>
<td>5</td>
<td>Adenocarcinoma grade 3</td>
<td>IA</td>
<td>S and C</td>
<td>NED</td>
<td>8.7</td>
</tr>
<tr>
<td>14</td>
<td>66</td>
<td>No</td>
<td>1</td>
<td>Normal</td>
<td>Complex mass</td>
<td>51</td>
<td>6</td>
<td>14</td>
<td>Adenocarcinoma grade 3</td>
<td>IA</td>
<td>S and C</td>
<td>NED</td>
<td>8.7</td>
</tr>
<tr>
<td>15</td>
<td>58</td>
<td>Yes</td>
<td>7</td>
<td>Normal</td>
<td>Complex mass</td>
<td>20</td>
<td>5</td>
<td>13</td>
<td>Granulosa cell tumor grade 2</td>
<td>IA</td>
<td>S</td>
<td>NED</td>
<td>8.7</td>
</tr>
<tr>
<td>16</td>
<td>59</td>
<td>No</td>
<td>1</td>
<td>Normal</td>
<td>Solid mass</td>
<td>118</td>
<td>7</td>
<td>5</td>
<td>Serous ovarian tumor of borderline malignancy</td>
<td>IA</td>
<td>S</td>
<td>NED</td>
<td>8.7</td>
</tr>
<tr>
<td>17</td>
<td>71</td>
<td>No</td>
<td>8</td>
<td>Palpable</td>
<td>Solid mass</td>
<td>103</td>
<td>7</td>
<td>13</td>
<td>Endometrioid carcinoma grade 2</td>
<td>IA</td>
<td>S and C</td>
<td>NED</td>
<td>8.7</td>
</tr>
<tr>
<td>18</td>
<td>60</td>
<td>No</td>
<td>1</td>
<td>Normal</td>
<td>Complex mass</td>
<td>91</td>
<td>5</td>
<td>23</td>
<td>Endometrioid adenocarcinoma grade 2</td>
<td>IB</td>
<td>S</td>
<td>NED</td>
<td>8.7</td>
</tr>
<tr>
<td>19</td>
<td>53</td>
<td>No</td>
<td>3</td>
<td>Normal</td>
<td>Complex mass</td>
<td>103</td>
<td>7</td>
<td>4</td>
<td>Clear cell adenocarcinoma grade 3</td>
<td>IA</td>
<td>S</td>
<td>NED</td>
<td>8.7</td>
</tr>
<tr>
<td>20</td>
<td>61</td>
<td>No</td>
<td>1</td>
<td>Normal</td>
<td>Complex mass</td>
<td>33</td>
<td>5</td>
<td>16</td>
<td>Serous ovarian tumor of borderline malignancy</td>
<td>IB</td>
<td>S and C</td>
<td>NED</td>
<td>8.7</td>
</tr>
<tr>
<td>21</td>
<td>71</td>
<td>No</td>
<td>11</td>
<td>Normal</td>
<td>Complex mass</td>
<td>20</td>
<td>6</td>
<td>47</td>
<td>Serous ovarian tumor of borderline malignancy</td>
<td>IB</td>
<td>S and C</td>
<td>NED</td>
<td>8.7</td>
</tr>
<tr>
<td>22</td>
<td>57</td>
<td>No</td>
<td>3</td>
<td>Normal</td>
<td>Complex mass</td>
<td>26</td>
<td>9</td>
<td>7</td>
<td>Granulosa cell tumor grade 1</td>
<td>IC</td>
<td>S</td>
<td>NED</td>
<td>11.0</td>
</tr>
<tr>
<td>23</td>
<td>64</td>
<td>Yes</td>
<td>7</td>
<td>Normal</td>
<td>Complex mass</td>
<td>122</td>
<td>5</td>
<td>5</td>
<td>Serous tumor of borderline malignancy</td>
<td>IC</td>
<td>S</td>
<td>NED</td>
<td>7.6</td>
</tr>
<tr>
<td>24</td>
<td>48</td>
<td>Yes</td>
<td>3</td>
<td>Palpable</td>
<td>Complex mass</td>
<td>141</td>
<td>7</td>
<td>-</td>
<td>Endometrioid adenocarcinoma grade 3</td>
<td>IC</td>
<td>S</td>
<td>NED</td>
<td>7.6</td>
</tr>
<tr>
<td>25</td>
<td>72</td>
<td>No</td>
<td>7</td>
<td>Normal</td>
<td>Solid mass</td>
<td>32</td>
<td>5</td>
<td>27</td>
<td>Serous ovarian tumor of borderline malignancy</td>
<td>IC</td>
<td>S and C</td>
<td>NED</td>
<td>7.6</td>
</tr>
<tr>
<td>26</td>
<td>64</td>
<td>No</td>
<td>1</td>
<td>Normal</td>
<td>Complex mass</td>
<td>34</td>
<td>4</td>
<td>21</td>
<td>Serous ovarian tumor of borderline malignancy</td>
<td>IC</td>
<td>S and C</td>
<td>NED</td>
<td>7.6</td>
</tr>
<tr>
<td>27</td>
<td>63</td>
<td>No</td>
<td>2</td>
<td>Normal</td>
<td>Complex mass</td>
<td>27</td>
<td>5</td>
<td>26</td>
<td>Papillary serous adenocarcinoma grade 1</td>
<td>IC</td>
<td>S</td>
<td>NED</td>
<td>7.6</td>
</tr>
<tr>
<td>28</td>
<td>53</td>
<td>No</td>
<td>2</td>
<td>Normal</td>
<td>Complex mass</td>
<td>10</td>
<td>4</td>
<td>6</td>
<td>Serous ovarian tumor of borderline malignancy</td>
<td>IC</td>
<td>S and C</td>
<td>NED</td>
<td>7.6</td>
</tr>
<tr>
<td>29</td>
<td>79</td>
<td>No</td>
<td>12</td>
<td>Normal</td>
<td>Complex mass</td>
<td>15</td>
<td>5</td>
<td>239</td>
<td>Endometrioid carcinoma grade 2</td>
<td>IA</td>
<td>S and C</td>
<td>NED</td>
<td>7.6</td>
</tr>
<tr>
<td>30</td>
<td>67</td>
<td>No</td>
<td>18</td>
<td>Normal</td>
<td>Complex mass</td>
<td>16</td>
<td>3</td>
<td>5</td>
<td>Adenocarcinoma grade 3</td>
<td>IA</td>
<td>S</td>
<td>NED</td>
<td>7.6</td>
</tr>
<tr>
<td>31</td>
<td>78</td>
<td>No</td>
<td>2</td>
<td>Palpable</td>
<td>Complex mass</td>
<td>30</td>
<td>5</td>
<td>11</td>
<td>Papillary serous adenocarcinoma grade 2</td>
<td>IA</td>
<td>S and C</td>
<td>NED</td>
<td>7.6</td>
</tr>
<tr>
<td>32</td>
<td>66</td>
<td>No</td>
<td>12</td>
<td>Complex mass</td>
<td>128</td>
<td>7</td>
<td>7</td>
<td>Serous cystadenocarcinoma grade 3</td>
<td>IA</td>
<td>S and C</td>
<td>NED</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>58</td>
<td>Yes</td>
<td>8</td>
<td>Normal</td>
<td>Complex mass</td>
<td>335</td>
<td>9</td>
<td>134</td>
<td>Mucoepidermoid carcinoma grade 3</td>
<td>IA</td>
<td>S</td>
<td>NED</td>
<td>7.6</td>
</tr>
<tr>
<td>34</td>
<td>45</td>
<td>Yes</td>
<td>8</td>
<td>Complex mass</td>
<td>355</td>
<td>9</td>
<td>1500</td>
<td>Adenocarcinoma grade 3</td>
<td>IA</td>
<td>S and C</td>
<td>NED</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>61</td>
<td>Yes</td>
<td>15</td>
<td>Normal</td>
<td>Complex mass</td>
<td>54</td>
<td>5</td>
<td>214</td>
<td>Endometrioid carcinoma grade 3</td>
<td>IC</td>
<td>S</td>
<td>NED, DOG</td>
<td>7.6</td>
</tr>
</tbody>
</table>

*Diagnoses: TVS, transvaginal sonography; MI, morphology index; S and C, chemotherapy; NED, no evidence of disease; DOG, dead from other causes; DO, dead of disease.*
cancer (18%) had a palpable abnormality on clinical examination. Nine patients with stage I invasive ovarian cancer had pre-operative CA-125 determinations, and antigen levels were elevated (>35 U/mL) in 1 patient (11%). Twenty-one of 44 primary ovarian cancers (48%) were detected on the first screen, and the remaining primary ovarian cancers were detected on subsequent screens. Four of 44 patients (9%) who had primary ovarian cancers detected by annual screening have died of disease. Three of those patients had stage III ovarian cancer at the time of their first or second screen and died of disease from 1.8 years to 7.1 years after diagnosis. One patient (No. 32) had a poorly differentiated stage IIA ovarian serous cystadeno carcinoma detected on the 12th screen and died of disease 1.3 years after she underwent surgical debulking and received carboplatin/taxol chemotherapy. Thirty-eight patients remain alive and well with no evidence of disease from 0.5 years to 15.8 years (mean, 5.3 years) after diagnosis, and 2 patients without evidence of disease died of other causes 3.1 years and 8.0 years after diagnosis.

Nine patients developed ovarian cancer within 12 months of a negative screen (false-negative results). Three of those patients had normal sized ovaries at the time of surgical exploration 3 months, 12 months, and 12 months after a normal screen but had extraovarian metastases resulting in a diagnosis of stage IIA ovarian cancer (1 patient) and stage IIIC ovarian cancer (2 patients). Six patients had increased ovarian volumes at the time of surgery from 2 months to 11 months after a normal screen and had stage IIC ovarian cancer (1 patient), stage IIIB cancer (1 patient), and stage IIIC cancer (4 patients). Seven of those patients had poorly differentiated ovarian carcinomas, and 2 had moderately differentiated tumors. Serum CA-125 determinations were obtained in all 9 of those patients at the time of surgery and were elevated (>35 U/mL) in 8 patients. All patients were treated with a combination of surgery and chemotherapy. Five patients were alive without evidence of disease from 0.5 years to 5.5 years after diagnosis, and 3 patients died of disease from 0.7 years to 7.0 years after diagnosis. One patient who had no evidence of disease died of a myocardial infarction 9.8 years after diagnosis.

Seven women had metastatic cancer to the ovary detected by screening (Table 4). It was believed that all of those women had a primary ovarian neoplasm prior to surgical exploration. Three of these patients had primary appendiceal cancer with metastases to the ovary and underwent hemicolectomy and ovarian tumor debulking. They remain alive without evidence of disease from 1 year to 6.3 years after treatment. Two patients had primary peritoneal cancer detected by the presence of paraovarian
fluid. Both of those patients had peritoneal and ovarian surface involvement by a poorly differentiated epithelial adenocarcinoma and had no evidence of ovarian stromal invasion. One patient remains alive with disease 1.7 years after diagnosis, and the other patient has no evidence of disease 3.7 years after surgery and chemotherapy. Finally, there was 1 patient with ovarian Four hundred fifty-six patients (1.8%) with nor-mal screens underwent hysterectomy and bilateral salpingo-oophorectomy for a variety of indications that were unrelated to screening. Ovarian volume and morphology were normal in all of these patients at the time of surgery, and there were no cases of ovarian neoplasia. There were 3746 postmenopausal women with 6513 unilocular cystic ovarian tumors who were followed at 3- to 6-month intervals by TVS without surgery. Duration of follow-up ranged from 4 months to 16.5 years (mean, 4.6 years). Spontaneous resolution occurred in 5381 of these cysts (83%), usually within 6 months, and no patient in this group has developed ovarian cancer.

The statistical definitions used in this investiga-tion are presented in Table 5. There were 51

<table>
<thead>
<tr>
<th>Term</th>
<th>Screen</th>
<th>Findings</th>
<th>No. of study patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positive (TP)</td>
<td>Positive</td>
<td>Histology confirms ovarian cancer</td>
<td>51</td>
</tr>
<tr>
<td>False positive (FP)</td>
<td>Positive</td>
<td>Benign ovarian histology</td>
<td>313</td>
</tr>
<tr>
<td>True negative (TN)</td>
<td>Negative</td>
<td>No evidence of disease 12 mo after negative screen</td>
<td>24,954</td>
</tr>
<tr>
<td>False negative (FN)</td>
<td>Negative</td>
<td>Ovarian cancer diagnosed within 12 mo of negative screen</td>
<td>9</td>
</tr>
</tbody>
</table>

* Sensitivity (TP/TP+FN) 85.0%, specificity (TN/TN+FP) 88.7%, positive predictive value (TP/(TP+FP) 14.0%, negative predictive value (TN/TN+FN) 99.9%.

patients with positive screens who had either primary ovarian cancer or cancer metastatic to the ovary (true-positive results). There were 313 patients with positive screens who had benign ovarian tumors (false-positive results). Likewise, there were 23,706 patients with negative screens, and 9 women developed ovarian cancer within 12 months of a negative scan (false-negative results). Using these data, the sensitivity of TVS screening was 85%, and the specificity was 98.7%. The positive predictive value (PPV) of an abnormal screen was 0.1401, and the negative predictive value (NPV) of a normal screen was 0.999. Screening statistics related to date of entry into the trial, family history, and menopausal status are presented in Table 6.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total no. of cases</th>
<th>1887 to 2001</th>
<th>2001 to present</th>
<th>No family history</th>
<th>Family history</th>
<th>Premenopausal</th>
<th>Postmenopausal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>25,327</td>
<td>16,242</td>
<td>9085</td>
<td>19,270</td>
<td>6057</td>
<td>7078</td>
<td>13,249</td>
</tr>
<tr>
<td>TP</td>
<td>51</td>
<td>23</td>
<td>28</td>
<td>42</td>
<td>9</td>
<td>7</td>
<td>44</td>
</tr>
<tr>
<td>FP</td>
<td>313</td>
<td>238</td>
<td>75</td>
<td>227</td>
<td>86</td>
<td>72</td>
<td>241</td>
</tr>
<tr>
<td>FN</td>
<td>9</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>TN</td>
<td>24,954</td>
<td>15,977</td>
<td>8977</td>
<td>18,996</td>
<td>5959</td>
<td>6998</td>
<td>17,956</td>
</tr>
<tr>
<td>Sen</td>
<td>0.85</td>
<td>0.861</td>
<td>0.849</td>
<td>0.975</td>
<td>0.75</td>
<td>0.875</td>
<td>0.846</td>
</tr>
<tr>
<td>Spec</td>
<td>0.987</td>
<td>0.992</td>
<td>0.992</td>
<td>0.988</td>
<td>0.986</td>
<td>0.989</td>
<td>0.986</td>
</tr>
<tr>
<td>PPV</td>
<td>0.140</td>
<td>0.088</td>
<td>0.271</td>
<td>0.166</td>
<td>0.096</td>
<td>0.088</td>
<td>0.164</td>
</tr>
<tr>
<td>NPV</td>
<td>0.9996</td>
<td>0.9997</td>
<td>0.9994</td>
<td>0.9997</td>
<td>0.9997</td>
<td>0.9998</td>
<td>0.9996</td>
</tr>
<tr>
<td>Screening, γ²</td>
<td>107.276</td>
<td>90,540</td>
<td>16,730</td>
<td>78,397</td>
<td>28,879</td>
<td>37,683</td>
<td>82,811</td>
</tr>
</tbody>
</table>

TP indicates true positive; FP, false positive; FN, false negative; TN, true negative; Sen, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value. The statistical evaluation of screening is based on the data presented in Table 5.
The screening algorithm was changed on January 1, 2001, such that patients with unilocular cystic ovarian tumors measuring _5 cm were followed sonographically at 6-month intervals rather than undergoing surgery. The PPV of screening increased from 8.8% (1987–2000) to 27.1% (2001–2006) as a result of this change. Likewise, the PPV of screening increased from 8.8% in premenopausal patients to 15.4% in postmenopausal patients. In patients receiving TVS screening, there have been 107,276 screening years and 10 deaths from ovarian cancer. Seven of the patients who died of ovarian cancer (4 with true-positive results and 3 with false-negative results) were compliant with the screening algorithm and were screened at yearly intervals. Two of the four women in the true-positive group who died of disease had stage III ovarian cancer at the time of their initial screen. There were 3 noncompliant patients who died of ovarian cancer. These patients returned to their local physicians with symptoms of abdominal swelling after having no screening for 21 months, 51 months, and 61 months. All 3 of those patients had stage III disease at the time of their diagnosis and died of disease from 1 year to 4.6 years after diagnosis.

The survival rate of patients with ovarian cancer in the annual screening group was 92.1% _ 7.9% at 2 years and 82.4% _ 17.6% at 5 years. When we excluded the 5 patients who had granulosa cell tumors and the 9 patients who had serous ovarian tumors of borderline malignancy, the survival rate was 89.9% _ 10.1% at 2 years and 77.2% _ 22.8% at 5 years. The survival rate of all patients with ovarian cancer in the study group, including those who had cancer detected by screening and those who were diagnosed >12 months after a negative screen by clinical examination, was 88.2% _ 11.8% at 2 years and 76.6% _ 23.4% at 5 years. This compares favorably with a 2-year survival rate of 70.7% _ 2.6% and a 5-year survival rate of 48.7% _ 3.5% for patients with ovarian cancer in the University of Kentucky Tumor Registry who did not receive screening (P < .001).

**DISCUSSION**

Analysis of data from nearly 20 years of screening allows us to reach certain conclusions about the benefits and limitations of TVS as a screening method for ovarian cancer. First, TVS is safe, time efficient, and well accepted by patients. In over 100,000 screens, <10 women have complained that TVS is uncomfortable. A complete screening examination usually takes from 5 minutes to 10 minutes, and no medical or surgical complications from TVS have been observed. When TVS is used in high-volume settings, its cost is well within the range of other accepted screening tests, and interobserver variation is minimal. Although there is a definite learning curve for technologists performing TVS, 1 or both ovaries were visualized in 84% of women, and ovarian tumor dimensions predicted by TVS correlated closely with recorded measurements at the time of surgery.

For a screening test to be effective, it should be sensitive and specific, and it should have both a high PPV and a high NPV. Furthermore, periodic screening should decrease the disease stage at detection and increase disease-specific survival in the screened population. The major limitations of TVS as a screening method for ovarian cancer are its moderate sensitivity and relatively low PPV. Although TVS screening accurately predicted the presence of cancer involving the ovary in 51 asymptomatic women, there were 9 patients who developed ovarian cancer within 12 months of a normal scan (false-negative results). Six of those patients had minimally enlarged ovaries at the time of surgery from 3 months to 12 months (mean, 8 months) after a normal scan but had extra ovarian
spread. Five of these 6 ovarian cancers were poorly differentiated. TVS did not detect an abnormality in these women, because their ovarian volume was increased minimally. Whether the addition of a serum CA-125 determination to TVS as a primary test in the screening algorithm would have resulted in the earlier detection in these women can not be answered from these data because CA-125 measurement was obtained as a secondary test only in those patients who had a persisting abnormality on TVS. However, serum CA-125 levels were elevated in 8 of those 9 patients (88%) at the time of surgery, and it is logical to assume that marker elevation would have preceded clinical detection in some of these women. Other screening trials that were designed to answer this question are in progress.\textsuperscript{7,13} In the current investigation, serum CA-125 levels were increased (>35 U/mL) at the time of detection in 13 of 15 patients (87%) who had stage III epithelial ovarian cancer but in only 3 of 15 patients (20%) who had stage I or II disease.

A second area of concern related to TVS screening for ovarian cancer is its relatively low PPV. Whereas TVS is accurate in identifying ovarian tumors, it is less effective in differentiating benign lesions from malignant lesions. In the current investigation, 14% of persisting complex ovarian tumors were malignant. Tumor morphology\textsuperscript{21–24} and serum biomarker patterns\textsuperscript{25–28} both have been useful in predicting the risk of malignancy in sonographically confirmed ovarian tumors. In the current investigation, all but 1 of the screen-detected ovarian malignancies were either solid tumors or cystic tumors with solid areas or papillary projections from the cyst wall. There were 153 unilocular cystic ovarian tumors that measured <5 cm in greatest dimension (MI, _4), and all were benign. In 2001, the screening algorithm at the University of Kentucky was changed, such that unilocular cystic ovarian tumors that measured _5 cm in greatest dimension were followed sonographically rather than removed surgically. Since that time, the PPV of TVS screening has increased to 27.1%, which is well within the range of other accepted screening tests, such as mammography and cervical cytology.\textsuperscript{29–31} None of these patients has developed ovarian cancer, thereby confirming the safety of following small unilocular ovarian cysts sonographically and avoiding surgery in these women. It is our current policy to follow all patients with unilocular cystic ovarian tumors that measure _5 cm in greatest dimension at 6-month intervals with TVS rather than proceeding with operative intervention.

The use of a single biomarker value to distinguish benign ovarian tumors from early-stage ovarian cancer has been problematic. In the current investigation, for example, serum CA-125 measurements were obtained at the time of surgery in 9 patients with stage I invasive epithelial ovarian cancer detected by screening and was elevated (>35 U/mL) in only 1 patient. Recent data suggest that serial marker determinations may be more effective than a single threshold value in identifying ovarian malignancies. Generally, serum CA-125 values rise over time in patients with ovarian cancer, whereas they remain stable or decrease in patients with benign ovarian tumors. Using a risk calculation based on progressively rising serum CA-125 levels, Skates and colleagues\textsuperscript{32} were able to increase the sensitivity of ovarian cancer detection from 62% to 86%. Therefore, serum CA-125 determinations at 2- to 4-week intervals can be helpful in establishing the risk of malignancy in a specific ovarian tumor.

Despite the aforementioned limitations, annual TVS screening decreases disease stage at detection and increases case-specific ovarian cancer survival. In the current trial, 82% of women who had ovarian cancer detected by screening had stage I or stage II disease versus 34% of women
in the unscreened historic control group (P < .0001). In 107,276 screening years, 53 primary ovarian cancers were detected (44 true-positive results and 9 false-negative results). Seven deaths occurred in women who were compliant with the screening algorithm. Two of those patients had advanced-stage disease at the time of their initial screen and died of disease after treatment with surgery and chemotherapy. The survival rate for all patients with invasive epithelial ovarian cancer in the screening group was 89.9% at 2 years and 77.2% at 5 years, which was significantly higher (P < .001) than the survival rate of patients with ovarian cancer in the control group who did not have screening (2-year survival rate, 70.9%; 5-year survival rate, 48.7%).

Ovarian cancer poses specific challenges for screening. Although ovarian cancer is curable when it is detected early, it is not common, and rates of progression, even among epithelial cancers, are variable. In this trial, ovarian cancer screening was performed at yearly intervals. However, it may be necessary to increase the frequency of screening in certain high-risk women. It should be possible, as more complete molecular genetic data concerning the etiology of ovarian cancer become available, to construct more accurate risk profiles for each patient and to match screening frequency to risk of malignancy. Finally, investigation must continue to identify proteins or other biomarkers that are specific to ovarian cancer that can be used for early diagnosis. This is particularly important for the detection of cancers that involve only the ovarian surface epithelium and do not produce ovarian enlargement, thus evading sonographic surveillance.

With more effective chemotherapy now available for patients with ovarian cancer, even a modest advance in the time to diagnosis should be associated with a significant survival advantage. In the absence of early detection, most women with ovarian cancer will continue to present with advanced-stage disease, for which the cost of treatment is high and the cure rate is extremely low. The protective effect of annual sonographic screening on ovarian cancer mortality observed in the current trial should only increase as more specific biomarkers are added to TVS in screening algorithms.

REFERENCES

Screening for Ovarian Cancer: The Possible Improvement by 3D Ultrasound and 3D Power Doppler

Asim Kurjak, Ulrich Honemeyer, Matija Prka

1 Department of Obstetrics and Gynecology, Medical School University of Zagreb, Croatia
2 Department of Mother and Child, Welcare Hospital, Dubai, United Arab Emirates

Correspondence: Ulrich Honemeyer, Specialist Obstetrics and Gynecology, Welcare Hospital, Department of Mother and Child Dubai, United Arab Emirates, Phone: +971505512615, e-mail: ulrich@welcarehospital.com

Abstract

In developed countries more women die annually from ovarian cancer than from all other gynecologic malignancies combined. The fact that the ovaries are deep within the pelvic cavity and difficult to palpate is an obstacle to early diagnosis, especially in peri-post menopausal women, the group with the highest incidence of the disease. Seventy percent of patients are not diagnosed with the disease until the cancer has metastasized beyond the ovaries and is at stage III or IV because of these reasons.

Patients with stage 3 or 4 have a 5-year survival rate of only 20-30%, compared with the 5-year survival of over 90% in patients with stage IA ovarian cancer, when disease is confined to the ovary. Given the burden of suffering associated with the development of ovarian cancer and the clear survival gradient related to the stage of disease at diagnosis, there has always been much enthusiasm for the development of effective screening methods/assays for the early detection of epithelial ovarian cancer.

Keywords: Screening methods, Early detection, Transvaginal sonography, Multimodal screening.

WHY TO SCREEN FOR OVARIAN CANCER?

In developed countries more women die annually from ovarian cancer than from all other gynecologic malignancies combined. For example, in the United States approximately 22,000 new cases are diagnosed each year, and 15,000 of these women will die of the disease. Nondescript signs and symptoms make it the seventh leading cause of cancer related deaths in women. In 2008, there were 21,650 cases reported which resulted in the deaths of 15,520 women in the United States.

Symptoms usually do not become apparent until the tumor compresses or invades adjacent structures, ascites develops, or metastases become clinically evident. However, studies surveying ovarian cancer patients demonstrate that over 95% of EOC patients had abdominal complaints for many months before their diagnosis. The fact that the ovaries are deep within the pelvic cavity and difficult to palpate is an obstacle to early diagnosis, especially in peri-post menopausal women, the group with the highest incidence of the disease. 70% of patients are not diagnosed with the disease until the cancer has metastasized beyond the ovaries and is at stage III or IV because of these reasons.

Patients with stage 3 or 4 have a 5-year survival rate of only 20-30%, compared with the 5-year survival of over 90% in patients with stage IA ovarian cancer, when disease is confined to the ovary. Given the burden of suffering associated with the development of ovarian cancer and the clear survival gradient related to the stage of disease at diagnosis, there has always been much enthusiasm for the development of effective screening methods/assays for the early detection of epithelial ovarian cancer.

There are several different types of ovarian cancers depending upon the cell type of origin. Epithelial cell ovarian cancer (EOC) constitutes 90% of ovarian cancers, while gonadal-stromal (6% occurrence), and germ cell (4% occurrence) tumors make up the rest of the incidence of ovarian cancer patients. The stages (I-IV) of ovarian cancer are determined by the extent of metastasis. Stage I EOC is confined to the
ovaries, stage II involves other pelvic structures. In stage III, the disease has spread beyond the pelvis into the upper abdominal cavity or into the draining nodal beds. Stage IV is defined as disease outside of the peritoneal cavity and often includes parenchymal liver lesions or malignant pleural effusions. Patients with stage I disease most commonly undergo bilateral oophorectomy, hysterectomy, and surgical staging including peritoneal biopsies, omentectomy, and pelvic and aortic lymph node dissection. In select cases of younger patients who wish to preserve fertility, only the affected ovary may be removed and a hysterectomy would not be performed.

Each cancer type typically metastasizes to different areas in the body. This phenomenon is called the “seed vs soil” hypothesis which was first observed by Stephen Paget in 1889.

The “seed vs soil” observation applies in ovarian cancer: the most common sites of metastasis are within the peritoneal cavity. This is explained by the fact that mesothelial cells that express mesothelin, line the walls of the peritoneal cavity as well as the organs within it. Gubbels et al have shown that MUC16 (CA 125), present on the surface of cancer cells, binds readily to mesothelin. The peritoneal dissemination of metastasis is facilitated by the clockwise flow of peritoneal fluid (PF).

DIFFICULTIES IN OVARIAN CANCER SCREENING

The ability to detect early-stage epithelial ovarian cancer by a simple test has long been desired, yet never achieved. Several aspects of ovarian cancer have led to the frustrations that have been encountered in attempts to screen for the disease.

The time required for localized disease to progress to dissemination depends on the tumor type; therefore the appropriate interval at which to pursue screening is at this point chosen arbitrarily. Other impediments to screening relate to the low prevalence of ovarian cancer in the general population. Therefore, a screening method should have a specificity of 99.6% to achieve a positive predictive value of 10%, i.e. to limit the number of unnecessary surgical procedures to 10 for each case of cancer detected. A specificity lower than this is likely to be unacceptable in the general population, although it may be acceptable to those with a positive family history of breast or ovarian cancer.

As ovarian cancer of epithelial cell origin (EOC) is the most common type, screening methods have to take into account the specific morphological and biochemical characteristics of this tumor group. The majority of EOC cases are sporadic in nature and occur in women with no known predisposing factors. Thus, in the general population, the overall risk of EOC is low (2-5%). Only a small percentage (5-10%) of EOC patients have a genetic predisposition to the disease. Ninety percent of these patients are carriers of mutated BRCA1 and/or BRCA2 genes, which are also implicated in hereditary breast cancer. These genes normally act as tumor suppressors and regulate cellular proliferation and DNA repair by maintaining chromosomal integrity. Mutations in these genes render the proteins unable to perform their intended functions. The lifetime risk of ovarian cancer for patients with BRCA1 mutations is 20% to 60%, and the risk for BRCA2 mutation carriers is 10% to 35%.

The normal ovarian surface epithelium (OSE) covers the surface of the ovary. OSE is a monolayered squamous-to-cuboidal epithelium which functions to shuttle molecules in and out of the peritoneal cavity, as well as participates in the rupture and repair that accompanies every ovulation. The OSE derive from the embryonic celomic epithelial cells which are a part of the mesoderm. The fallopian tube, uterus, and endocervix are derived from the Mullerian duct which is an invagination of the celomic epithelium. It is hypothesized that OSE cells retain the ability to differentiate into four major histological subtypes, which could explain the distinct histological EOC subtypes. There are four common sub-types of ovarian cancer of epithelial cell origin (EOC), including serous (fallopian tube-like), endometrioid (endometrium-like), mucinous (endocervical-like), and clear cell carcinoma (mesonephros-like).

The differentiation of OSE cells from cuboidal epithelial cells to a mesenchymal phenotype that is characteristic of Mullerian duct derived tissues, is called epithelial-mesenchymal transition (EMT). The occurrence of EMT serves the purpose to aid cells in movement during embryo tissue generation, tissue regeneration after wounding, and obviously plays a role in the development of cancer.
OSE cells express low levels of the mucin MUC16 (CA125). Mullerian duct derived tissues express high levels of MUC16 (CA125), as do ovarian tumors. MUC16 (CA125) over-expression in ovarian tumors is an important marker for progression and regression of EOC.

The expression of markers that are associated with those of Mullerian duct derived tissue are found in ovarian inclusion cysts. Inclusion cysts are known to be the site of many neoplasms. The OSE lining in inclusion cysts expresses high levels of EOC markers MUC16 (CA125) and CA19-9. The hypothesis that epithelial ovarian cancer may derive from inclusion cysts is based upon the Incessant Ovulation Theory, first proposed by Fathalla in 1971.

Higher ovulatory activity is associated with an increased accumulation of inclusion cysts and invaginations of the OSE, which provide a hospitable environment for tumor cell growth. This theory is supported by epidemiological data demonstrating that women who have been on oral contraceptives, or who have been pregnant and/or breastfeeding, have a decreased risk of ovarian cancer.

Dubeau in 1999 first proposed the hypothesis that the fimbriae of the fallopian tubes, which are in close contact with the surface of the ovary during oocyte collection, and sometimes adhere to the surface of the ovary due to inflammation, are a prime site for the development of metaplasia.

**ATTEMPTS TO SCREEN—SOME LESSONS LEARNED**

During the last 15 years, large prospective studies of screening for ovarian cancer have been performed. Two distinct strategies have emerged, one based on ultrasound as the primary test, and the other involving the serum tumor marker CA 125 screening with ultrasound as the secondary test (multimodal screening). Tables 1 and 2 summarize the prospective ovarian cancer screening studies in the general population. If we exclude those which used trans-abdominal ultrasound, an abandoned screening strategy due to unacceptably high rate of false positive results, several important lessons could be learned.

As seen in the Tables 1 and 2, the data suggest that sequential multimodal screening has greater specificity and positive predictive value compared to strategies based on transvaginal ultrasound alone. For each case of ovarian cancer detected, five women underwent surgery in the multimodal studies compared to 24 women in the studies using ultrasound alone. However, transvaginal ultrasound as a first line test may offer higher sensitivity for early stage disease given that 23/37 (62.2%) cancers detected using ultrasound alone were stage I, compared to 8/19 (42.1%) cancers detected by the multimodal strategy. An ultrasound-based strategy may have a greater impact on ovarian cancer mortality, albeit at a higher price in terms of surgical intervention for false positive results.

The Tables 1 and 2 address most relevant studies published until 2003. Our own ovarian cancer screening trial, which started in January 2001 will be described at the end of this chapter. The developments that followed since 2003 are best summarized in reference to the screening tests, target populations and newly published trials. The possible role of 3D ultrasound technology, especially 3D power Doppler imaging, in early and accurate detection of ovarian malignancy will be discussed as well.

**SCREENING TESTS**

Screening for ovarian cancer has been based on strategies using serum tumor markers or transvaginal ultrasound images of the ovaries, or a combination of both.

**SERUM TUMOR MARKERS**

In epithelial ovarian cancer, a number of tumor markers have been identified. Serum CA 125 continues to be the tumor marker most extensively used in ovarian cancer screening. CA125 itself is a repeating peptide epitope on
the large molecular weight mucin, MUC16. This mucin is expressed at low levels by normal ovarian surface epithelium and is overexpressed by EOC tumor cells.
Tumor cells secrete mucin (MUC16) into the peritoneal fluid (PF) and from the abdominal cavity this mucin leaks into the bloodstream and can then be detected via the CA125 serum assay.

Although CA 125 is elevated (>35 U/ml) in more than 80% of patients with epithelial ovarian cancer, it is

---

**Table 1: Prospective ovarian cancer screening studies using ultrasound as the primary test in the general population**

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion criteria</th>
<th>Screening strategy</th>
<th>No. screened</th>
<th>No. of invasive epithelial ovarian cancers detected</th>
<th>No. of positive screens</th>
<th>No. of positive screens/cancer detected</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ULTRASOUND (US) APPROACH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van Nagell et al.</td>
<td>Age &gt; 50 years and postmenopausal women</td>
<td>TVS</td>
<td>14409</td>
<td>11 (6)</td>
<td>180</td>
<td>16.4</td>
</tr>
<tr>
<td>Hayskki et al.</td>
<td>Age &gt; 50 years</td>
<td>TVS</td>
<td>23451</td>
<td>3 (3)</td>
<td>288</td>
<td>?</td>
</tr>
<tr>
<td>Campbell et al.</td>
<td>Age &gt; 45 years with positive family history</td>
<td>TAS</td>
<td>5479</td>
<td>2 (3)</td>
<td>320</td>
<td>16.3</td>
</tr>
<tr>
<td>Goezweny et al.</td>
<td>Age 39-78, postmenopausal</td>
<td>TAS</td>
<td>1064</td>
<td>1 (1)</td>
<td>Not precised</td>
<td></td>
</tr>
<tr>
<td><strong>GREY-SCALE US and CDI (LEVEL 1 SCREEN)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vuuoto et al.</td>
<td>Aged 50-64 years</td>
<td>TVS and CDI</td>
<td>1364</td>
<td>1 (1)</td>
<td>5</td>
<td>?</td>
</tr>
<tr>
<td>Kurjak et al.</td>
<td>Aged 40-71 years</td>
<td>TVS and CDI</td>
<td>5013</td>
<td>4 (4)</td>
<td>38</td>
<td>9.5</td>
</tr>
<tr>
<td><strong>GREY-SCALE US (LEVEL 2 SCREEN)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saito et al.</td>
<td>Age &gt; 50 years or &gt; 30 with positive family history</td>
<td>TVS and tumor markers</td>
<td>51550</td>
<td>10 (6)</td>
<td>324</td>
<td>20.3</td>
</tr>
<tr>
<td>Pakes et al.</td>
<td>Aged 50-64</td>
<td>TVS and CA125</td>
<td>2663</td>
<td>1 (1)</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Holbert et al.</td>
<td>Postmenopausal</td>
<td>TVS and CA125</td>
<td>478</td>
<td>1 (1)</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TAS = transabdominal ultrasound; TVS = transvaginal ultrasound; CDI = Color Doppler imaging

*aThe borderline-granulosa tumors detected are shown in parenthesis.
*bOnly invasive epithelial ovarian cancers included.
*cOnly 95 women consented to surgery and there are no follow-up details on the remaining.
*dOnly 11 of these women underwent surgery.
*eStudies used TBS are excluded.

---

**Table 2: Prospective ovarian cancer screening studies using serum CA 125 as the primary test in the general population**

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion criteria</th>
<th>Screening strategy</th>
<th>No. screened</th>
<th>No. of invasive epithelial ovarian cancers detected</th>
<th>No. of positive screens</th>
<th>No. of positive screens/cancer detected</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CA 125 ONLY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Einhorn et al.</td>
<td>Age &gt; 40 years</td>
<td>Serum CA 125</td>
<td>5550</td>
<td>6</td>
<td>175</td>
<td>29.2</td>
</tr>
<tr>
<td><strong>MULTIMODAL APPROACH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jacobs et al.</td>
<td>Age &gt; 45 years postmenopausal</td>
<td>RCT</td>
<td>10558</td>
<td>6</td>
<td>28</td>
<td>4.6</td>
</tr>
<tr>
<td>Jacobs et al.</td>
<td>Age &gt; 45 years postmenopausal</td>
<td>Serum CA 125 and TAS, TVS, or CA 125</td>
<td>22000</td>
<td>11</td>
<td>41</td>
<td>3.7</td>
</tr>
<tr>
<td>Adonakis et al.</td>
<td>Age &gt; 45 years</td>
<td>Serum CA 125 and TVS, or CA 125</td>
<td>2000</td>
<td>1 (1)</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Grover et al.</td>
<td>Age &gt; 40 years or with positive family history (3%)</td>
<td>Serum CA 125 and TAS, TVS, or CA 125</td>
<td>2500</td>
<td>1</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RCT = randomized controlled trial

"Only multimodal approach studies included."
only in 25% sensitive for early stage disease. Indeed, its value as an initial screening tool is limited since picking up stage III disease at an earlier time may not alter outcome. To improve further the performance of CA 125 as a screening tool, an algorithm incorporating age, rate of change of CA 125 and absolute levels to calculate an individual’s risk of ovarian cancer has been described.

This increases the sensitivity of CA 125 in comparison with a single cutoff value, because women with normal but rising levels are identified as being at increased risk. This approach was an integral part of the multimodal screening strategy adopted in the St Bartholomew’s Hospital randomized control trial, published in the year 2000.

Because CA125 levels are elevated in less than half of the cases in early-stage ovarian cancers, underscoring the lack of sensitivity to diagnose curable disease, CA125 appears not suitable to be used as a screening test, but mainly as a measure of disease progression, regression, and predictor of recurrence during treatment for EOC.

Another limitation of serum CA 125 represents that it is not specific for ovarian carcinoma because it can be elevated in many benign conditions such as endometriosis, uterine fibroids, pelvic inflammatory disease, ascites or pleural effusion. It is now known that the CA 125 antigen carries two major antigenic domains classified as A (the domain binding monoclonal antibody OC125) and B (the domain binding monoclonal antibody M). New generation assays, combining monoclonal antibodies to the two distinct regions of the molecule, have been shown to have improved specificity for the detection of early ovarian cancer.

Lysophosphatidic acid (LPA), a bioactive phospholipide with mitogenic and growth factor-like activities, is a tumor marker which was considered promising in ovarian cancer screening. In a small pilot series plasma LPA levels were elevated in 9 out of 10 patients with stage I ovarian cancer, 24 of 24 patients with stage II, III and IV ovarian cancer, and all 14 patients with recurrent ovarian cancer.

In comparison, among a subset of patients with ovarian cancer, only 28 out of 47 had elevated CA 125 levels, including 2 of 9 patients with stage I disease. Larger studies on the use of LPA in primary screening—perhaps in combination with other procedures, such as transvaginal ultrasound—for earlier detection and improved outcome for patients with ovarian cancer are in demand.

“The use of multiple novel tumor biomarkers for the detection of ovarian carcinoma in patients with a pelvic mass” was the title of study produced by Moore et al in 2008: Serum and urine samples were obtained preoperatively from women undergoing surgery for an adnexal mass. The samples were analyzed for levels of CA 125, SMRP, HE4, CA72-4, activin, inhibin, osteopontin, epidermal growth factor (EGFR), and ERBB2 (Her2) and were compared to final pathology results. Two hundred and fifty-nine patients with adnexal masses were enrolled. Of these, 233 patients were eligible for analysis with 67 invasive epithelial ovarian cancers and 166 benign ovarian neoplasms. In the analysis, HE4 had the highest sensitivity for detecting ovarian cancer as a single tumor marker, especially for Stage I disease. Combined CA 125 and HE4 were a more accurate predictor of malignancy than either alone.

Anderson et al, in January 2010, published a nested case-control study, assessing the lead time of selected ovarian cancer biomarkers which are identified as potential ovarian cancer biomarkers: CA 125, human epididymis protein 4 (HE4), mesothelin, B7-H4, decoy receptor 3 (DcR3), and spondin-2 have. Except for CA 125, their behavior in the prediagnostic period had not been evaluated. As per their results, smoothed mean concentrations of CA125, HE4, and mesothelin (but not of B7-H4, DcR3, and spondin-2) began to increase (visually) in cancer patients relative to control subjects approximately 3 years before diagnosis but reached detectable elevations only within the final year before diagnosis. The authors concluded that serum concentrations of CA125, HE4, and mesothelin may provide evidence of ovarian cancer 3 years before clinical diagnosis, but the likely lead time associated with these markers appears to be less than 1 year.

Transvaginal ultrasound is used in most screening strategies either as the sole screening modality or as a secondary test after primary screening with serum CA 125 (multimodal screening). As data regarding outcome accumulate with long-term follow-up of the participants of the early screening trials, it has been possible to define further risk of ovarian cancer associated with various ultrasound findings.

Particular results of the largest ultrasound-based ovarian cancer screening project from University of Kentucky might have a definitive impact on design of future ovarian cancer screening in the general population. Van Nagell et al established that unilocular ovarian cysts less than 10 cm in diameter, found in
256 out of 7705 (3.3%) asymptomatic women aged more than 50 years, were associated with a minimal risk for ovarian cancer because there were no cases of ovarian carcinoma during a 5-year follow-up period. In contrast, 7 out of the 250 women in the same study with complex cystic ovarian tumors, including wall abnormalities or solid areas, had ovarian carcinoma suggesting that these morphologic appearances are associated with a significant risk for malignancy.

In many screening algorithms, volume cut-offs are used in addition to morphology characteristics to identify women for intensive surveillance. Based on the data of 58,673 observations of ovarian volume, authors from Kentucky concluded that the upper limit of normal for ovarian volume is 20 cm$^3$ in premenopausal women and 10 cm$^3$ in postmenopausal women. Such data are very valuable in determining optimal strategies for operative intervention.

Recently, Kurman et al suggested an approach to early detection of ovarian cancer focusing on low volume rather than low stage of disease, to intercept the more aggressive tumors like high-grade serous carcinoma, malignant mixed mesodermal tumors (carcinosarcomas), and undifferentiated carcinomas, which account for most ovarian cancers. According to this research group, a more rational approach to early detection of ovarian cancer should focus on low volume rather than low stage of disease.

Postmenopausal women from the general population with an elevated serum CA 125 level but normal ovarian morphology on ultrasound were found to have a cumulative risk of ovarian cancer during a median follow up of 6.8 years, of 0.15%, which was similar to 0.22% of the entire population of 22,000 women. In contrast, those with an elevated serum CA 125 level and abnormal ovarian morphology on ultrasound had a significantly increased cumulative risk of 24%. Using ovarian morphology to interpret pelvic ultrasound images has been shown to increase sensitivity, and use of morphology scoring index for complex ovarian tumors may improve the positive predictive value of a multimodal screening strategy.

In a 2008 published Korean study, 202 patients who underwent surgery for ovarian tumors were reviewed retrospectively from September 2000 to July 2006. In all patients, the morphology index (MI) score and serum CA-125 level were measured preoperatively. The association of the final pathologic diagnosis with the MI score and serum CA 125 level were examined. The sonographic MI system was an accurate and simple method to differentiate a malignant tumor from a benign ovarian tumor. The accuracy of the sonographic MI system improved when the serum CA 125 level was considered and ovarian teratomas were excluded.

In the United Kingdom, a trial called UKCTOCS is looking at ovarian cancer screening in women in the general population. Between 2001 and 2005, a total of 202 638 post-menopausal women aged 50-74 years were randomly assigned to no treatment (control; n = 101 359); annual CA 125 screening (interpreted using a risk of ovarian cancer algorithm) with transvaginal ultrasound scan as a second-line test [multimodal screening (MMS); n = 50 640]; or annual screening with transvaginal ultrasound (USS; n = 50 639) alone in a 2:1:1 ratio using a computer-generated random number algorithm. In interpretation of the results, the authors consider the sensitivity of the MMS and USS screening strategies as encouraging. Specificity was higher in the MMS than in the USS group, resulting in lower rates of repeat testing and surgery. This in part reflects the high prevalence of benign adnexal abnormalities and the more frequent detection of borderline tumours in the USS group. The prevalence screen could establish that the screening strategies are feasible. The results of ongoing screening are awaited so that the effect of screening on mortality can be determined.

The first prospective randomized report of a multimodal ovarian cancer screening originates from a Japanese research group: Asymptomatic postmenopausal women were randomly assigned between 1985 and 1999 to either an intervention group (n = 41,688) or a control group (n = 40,799) in a ratio of 1:1, with follow-up of mean 9.2 years, in Shizuoka district, Japan. The original intention was to offer women in the intervention group annual screens by gynecological examination [sequential pelvic ultrasound (US) and serum CA125 test]. Women with abnormal US findings and/or raised CA125 values were referred for surgical investigation by a gynecological oncologist. The proportion of stage I ovarian cancer was higher in the screened group (63%) than in the control group (38%), which did not reach statistical significance (P =
TARGET POPULATIONS

Participants for ovarian cancer screening trials are recruited from general and high-risk populations on the basis of risk factors for the disease.

GENERAL POPULATION

Age and Menopausal Status

The majority of ovarian cancers occur in the general population, and age greater than 50 years and postmenopausal status have been used to define those eligible for screening. According to the FIGO report 2001,\(^6\) appearance of ovarian cancer was most common among women in early postmenopause, at average age of 54 years. Law et al.\(^6^1\) used national statistics to determine the number of years of life lost through deaths from a particular cancer at each age. They concluded that screening would be most effective (i.e. associated with the largest number of years of life saved per person screened) if done 5 years before loss of life peak. The peak occurred in ovarian cancer during the age range 55-59 years, and the authors’ argument provides further justification for using 50 years as the cutoff to commence population screening.

HIGH-RISK POPULATION

Family History and/or Genetic Predisposition

Approximately 5-10% of ovarian cancers are inherited. Mutations in BRCA1 and BRCA2 genes account for about 75% of families with a highly penetrant, dominantly inherited breast or ovarian cancer family history. Recent estimates of the lifetime risk for ovarian cancer in women harboring a BRCA1 mutation are 40-60%.\(^6^2\) Various studies have put forward schemes for stratifying women into different risk categories of risk for breast and ovarian cancer by virtue of a family history, genetic predisposition or both. Pharoah et al.\(^6^3\) reviewed the relevance of family history in defining the target population for familial ovarian cancer screening, and proposed the adoption of a unified management strategy based on eligibility criteria from UK National Familial Ovarian Cancer Screening Study (Table 3). A survey by Vasen et al.\(^6^4\) of the European Familial Breast Cancer Collaborative Group found that the following high-risk populations were offered ovarian cancer screening: BRCA1 and BRCA2 mutation carriers; members of breast/ovarian cancer families; and, in some centers, members of «breast cancer only» families with an early onset of breast cancer.

Table 3: Eligibility criteria for the UKCCCR National Familial Ovarian Cancer Screening Study\(^6^0\)

<table>
<thead>
<tr>
<th>Eligibility Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>An eligible woman must be over 25 years of age and a first degree relative of an affected member of an “at risk” family. At risk families are defined by the following criteria:</td>
</tr>
<tr>
<td>1. Two or more first degree relatives(^a) with ovarian cancer.</td>
</tr>
<tr>
<td>2. One first degree relative with ovarian cancer and one first degree relative with breast cancer diagnosed under 50 years of age.</td>
</tr>
<tr>
<td>3. One first degree relative with ovarian cancer and two first or second degree relatives(^b) with breast cancer diagnosed under 60 years of age.</td>
</tr>
<tr>
<td>4. An affected individual with one of the known ovarian cancer predisposing genes.</td>
</tr>
<tr>
<td>5. Three first degree relatives with colorectal cancer with at least one diagnosed before the age of 50 years and at least one first degree relative with ovarian cancer.</td>
</tr>
</tbody>
</table>

\(a\) A first degree female relative is mother, sister or daughter.

\(b\) A second degree female relative is grandmother, grand-daughter, aunt or niece.
OVARIAN CANCER SCREENING TRIALS

Clinical trials of ovarian cancer screening have involved strategies using ultrasound alone, and a multimodal approach with CA 125 as a primary test and ultrasound as a secondary test. Prospective studies have involved both the general and high-risk populations.

GENERAL POPULATION

Ultrasound Screening

In the evaluation of data from the 2000 University of Kentucky trial, the results of annual transvaginal ultrasound screening performed on 14,469 asymptomatic women aged 50 years or more and women aged 25 years or more with a family history of ovarian cancer were reported.23 Hundred and eighty patients with persisting transvaginal abnormalities were subjected to a surgical intervention. 17 primary ovarian cancers were detected of which 11 were epithelial ovarian cancers (EOC), three were granulosa cell tumors, and three were borderline tumors. Of the EOC, 5 were stage I, 3 were stage II and 3 were stage III. In this study, transvaginal ultrasound (TV US) as a screening modality was associated with sensitivity of 81%, specificity of 98.9%, positive predictive value of 9.4%, and negative predictive value of 99.97% for detection of all primary ovarian cancers. The survival of patients with EOC in the annually screened population was 92.9% at 2 years, and 83.6% at 5 years. What is encouraging about these results is that annual TV US screening appeared to achieve the primary goal of earlier detection of the disease, which translates into a reduction in mortality associated with ovarian carcinoma. On the other hand, data from this study suggested that in certain cases, length of time required for ovarian cancer to progress from a localized sonographically detectable tumor to widespread regional disease is quite short. In four patients in the false-negative group, disease progression from sonographically normal ovaries to stage II or III ovarian cancer occurred in less than 12 months. Authors stated that for future screening algorithms, a screening interval of 6 months should be taken into consideration. In 2000, the Japanese ovarian cancer screening trial was published: 51,550 women aged 30 years or more attending for annual cervical screening underwent TV US screening for ovarian cancer.31 Three hundred and twenty-four women with masses of more than 60 mm in diameter or with a mixed echo pattern or persistently raised tumor markers underwent laparotomy. Twenty-two primary ovarian tumors and two metastatic tumors were detected. Of the 22 primary tumors, 16 were EOCs, four were borderline malignancies and two were germ cell tumors. 11 (68.7%) of the EOCs were stage I, with tumor markers positive in 5 (45.4%) of the 11 cases. The positive predictive value of the screening strategy was 4.9%; in other words, 20 operations were undertaken for each detected case of ovarian cancer. As no follow-up data were reported on any of the trial participants, it is difficult to assess the sensitivity of the screening strategy. Before the onset of the screening, the authors noted that only 29.7% out of 35 cancers diagnosed in the department, were stage I, while after the trial was initiated, 58.8% of 85 ovarian cancers treated were stage I.

Multimodal Screening

One of the most active groups in screening for ovarian malignancy led by Jacobs, reported the results of the first completed randomized trial of ovarian cancer screening.35 This study which was published in 1999, randomized asymptomatic postmenopausal women aged 45 years or older to no screening (n = 10,977) or to annual multimodal screening for 3 years (n = 10,958). In the screening group 29 women with elevated CA 125 values and abnormal ultrasound findings were referred for surgical investigation. All 6 ovarian cancers detected were EOCs; 3 were stage I and 3 were stage III. The authors found a high positive predictive value of 20.7% with this schema and were encouraged by a longer median survival (72.9 months) in women with ovarian cancer in the screened group when compared to the control group (41.8 months). The mortality rates, however, were not significantly different between the groups. The authors concluded that the results do not justify ovarian cancer screening in the general population but do support the need for a larger randomized trial
that is powered to assess the impact of screening on mortality.

The Kentucky Ovarian Cancer Screening Trial confirmed that screening can detect ovarian cancer at an earlier stage than it is normally detected without screening. It also established the fact that the combination of serum CA 125 with transvaginal sonography (TVS) is probably more effective than TVS alone. The study design suggested that if the ultrasound was abnormal, a repeat TVS in four weeks was performed. If the repeat ultrasound was abnormal, CA 125 blood test and morphology indexing (MI) of form and structure of the ovarian mass was done. To improve accuracy in differentiating a benign ovarian tumor from ovarian cancer, MI was used to identify certain patterns that are associated with benign or noncancerous tumors. If the patient’s CA 125 was normal and the morphology index indicated a benign tumor, the patient was considered not to need surgery and was followed periodically with repeat ultrasound.⁶⁵

Both the Kentucky trial and the trial from the United Kingdom (UKCTOCS) detected ovarian cancer at a significantly earlier stage than when women did not have screening. The University of Kentucky Ovarian Cancer Screening Program is an ongoing trial; results from this trial were published in 2007 in the journal Cancer. Of women whose ovarian cancer was detected by screening, 82 percent had stage I or II disease compared to 30 percent of women in the unscreened population. Without screening, about 70 percent of women presented with stage III or IV disease. This is important to note because only 30 percent of women with advanced ovarian cancer will be alive in five years after treatment and two-thirds of them will still have disease that cannot be cured. Therefore, the ultimate cure rate for a woman with advanced ovarian cancer is only about 10 percent. So clearly, something needs to be done to increase early detection.

**HIGH-RISK POPULATION**

For women with a known germ line BRCA 1,2 mutation or with a family history suggesting a significant possibility of a genetic predisposition to ovarian cancer, the appropriate screening strategy remains undefined. In several studies, most authors advocate screening using TV US and serum CA 125 in patients who elect to delay or decline prophylactic oophorectomy. However, there is no consensus concerning the appropriate interval for screening.

Karlan et al reported the results of an ovarian cancer screening program launched in 1991, involving 1261 women aged over 35 years with a family history of ovarian, breast, colon or endometrial carcinoma, or a personal history of breast cancer.⁶⁶ Screening with TV US, color Doppler imaging and CA 125 was initially performed biannually until 1995, and annually thereafter. Two tumors of low malignant potential, on stage I EOC and 7 cases of primary peritoneal serous papillary carcinoma were diagnosed. Ultrasound abnormalities triggered surgical exploration in all three cases of ovarian disease. In 2 out of 7 cases, elevated levels of CA 125 were the harbinger of peritoneal serous papillary carcinoma, in two, abnormal ultrasound findings prompted diagnosis, and three developed interval cancers 5, 6 and 16 months after screening. At least three of the patients with primary peritoneal cancer carried mutations of the BRCA1 gene. Multifocal peritoneal serous papillary carcinoma may be a phenotypic variant of familial ovarian cancer, and screening strategies for these women cannot rely on ultrasound and CA 125 testing to detect early disease.

**OVARIAN CANCER—THE ROLE OF 3D ULTRASOUND AND 3D POWER DOPPLER IMAGING**

Improvements in ultrasound technology such as 3D volume acquisition and 3D power Doppler imaging may have clinical utility in a more reliable identification of an abnormal ovarian vascularity and architecture. 3D volume acquisition allows for careful evaluation of the internal surfaces of cyst walls for excrescences otherwise not appreciated by 2D ultrasound.⁶⁷,⁶⁸ While the addition of 3D power Doppler provides a new tool for measuring the quality of ovarian tumor angiogenesis,⁶⁹ improving accurate diagnosis of ovarian malignancies,⁷⁰ its clinical value for the early detection of ovarian carcinoma has yet to be determined.

**WHAT DOES 3D ULTRASOUND ADD?**
In the pioneer work, Bonilla-Musoles et al tried to determine whether 3D ultrasound may offer advantages over 2D ultrasound as a screening tool for the evaluation of ovarian lesions. Seventy-six women with ovarian masses first detected with 2D ultrasound were then evaluated with 3D ultrasound. The 3D sonographic criteria, used for diagnosing ovarian malignancy were based on the morphologic scoring system for 2D transvaginal ultrasound examinations proposed by different authors. A score greater than 4 caused suspicion of a malignant ovarian mass. The images were dissected in the three perpendicular planes, and the areas indicative of malignancy, as suggested by 2D ultrasonography, were determined to be either negative or positive and confirmatory. Five lesions observed on 2D ultrasound were suspected to be malignant. 3D sonography identified four of these lesions as malignant. The remaining one suspected to be malignant on 2D ultrasound was diagnosed as endometriosis with 3D sonography. One additional ovarian carcinoma was diagnosed by 3D scanning. Two of the malignant lesions were FIGO stage IA. The other tumors were FIGO stages IC, IIC, and IIIB, respectively. Authors stated that observation of papillary projections (especially those less than 3 mm), characteristics of cystic walls, and the extent of capsular infiltration was superior with 3D ultrasound in comparison to conventional 2D sonographic measurements, as was the calculation of ovarian tumor volume. They also pointed out that eventually 3D ultrasound imaging will allow diagnosis of ovarian malignancy at an earlier stage than it is possible with currently established diagnostic techniques.

**ADVANTAGES OF 3D POWER DOPPLER IMAGING**

There are two potential advantages of this new imaging modality: more accurate visualization of ovarian tumor neovascularization and more effective detection of stage I disease.

**More Accurate Visualization of Ovarian Tumor Neovascularization**

In order to determine whether three-dimensional power Doppler can improve the ability to differentiate benign from malignant ovarian masses, Kurjak et al performed transvaginal color Doppler and 3D power Doppler analysis on 120 patients with ovarian lesions. As a result, in each of 11 ovarian malignancies, preoperative diagnosis by 3D power Doppler was confirmed by histopathology. Transvaginal color Doppler missed one case of serous cystadenocarcinoma, while 3 benign lesions (dermoid cyst, ovarian fibroma, and ovarian cystadenofibroma) were considered false positive. In a case of cystadenofibroma, 3D power Doppler findings were falsely positive. Authors emphasized that irregular and randomly dispersed vessels with complex branching, depicted by 3D power Doppler imaging, were indicative for ovarian malignancy. Such qualitative analysis of the tumor vasculature architecture had a sensitivity, specificity, and positive predictive value (PPV) of 100, 99.08 and 91.67% in detection of ovarian malignancy, respectively. In a study published by Cohen et al, 71 women with a known complex pelvic mass were referred for a preoperative ultrasound evaluation with both two-dimensional gray-scale and 3D power Doppler ultrasound. All the women underwent surgical exploration, and 14 had ovarian cancer. Two-dimensional gray-scale ultrasound identified 40 masses as suspicious for cancer, including all 14 malignancies, yielding a sensitivity, specificity, and PPV of 100, 54 and 35% respectively. However, evaluation with 3D power Doppler identified only 28 cases as suspicious (including all cancers), resulting in a sensitivity, specificity, and PPV of 100, 75, and 50% respectively. Even though all malignancies were correctly identified by both 2D and 3D imaging, the specificity was significantly improved with the addition of 3D power Doppler. This improved diagnostic accuracy, authors stated, may promote improved patient care by separating complex benign masses from ovarian cancer, therefore facilitating appropriate physician referral.

Despite the inability of currently available screening algorithms to achieve the desired positive predictive value (PPV) of 10, there may be an advantage in producing a stage migration to lower stages at the time of diagnoses, thereby resulting in improved survival. Equally important recent studies have demonstrated that women who have their initial surgery performed by gynecologic oncologists, and women who have their surgeries at centers experienced in the treatment of ovarian cancer have higher survival rates. A cost-
effectiveness analysis conducted by Bristow et al. revealed that the strategy of expert center referral had an overall cost per patient of $50,652 and had an effectiveness of 5.12 quality-adjusted life years (QALYs). The strategy of referral to a less experienced center carried an overall cost of $39,957 and had an effectiveness of 2.33 QALYs. The expert center strategy was associated with an additional 2.78 QALYs at an incremental cost of $10,695 but was more cost-effective, with a cost-effective ratio of $9893 per QALY compared with $17,149 per QALY for the less experienced center referral strategy.

Kupesic and Kurjak reported already in 2000 on the use of contrast-enhanced, 3D power Doppler ultrasound in the differentiation of benign and malignant adnexal lesions. A total of 45 patients with complex adnexal lesions of uncertain malignancy at transvaginal B mode and/or color Doppler ultrasound were prospectively evaluated with 3D power Doppler before and after injection of contrast agent. There were 12 cases of ovarian malignancy and 33 benign adnexal lesions. Of the 12 ovarian cancers, seven (58.3%) showed vascular distribution suggestive of malignancy at non-enhanced 3D power Doppler imaging. After injection of contrast agent, a penetrating vascular pattern and/or a mixed penetrating and peripheral pattern were detected in all cases of ovarian malignancy. One cystadenofibroma demonstrated penetrating vessels at initial scan, whereas two benign lesions (fibroma and cystadenofibroma) were misdiagnosed as malignant with contrast-enhanced 3D power Doppler. The use of a contrast agent with 3D power Doppler showed diagnostic efficiency (95.6%) that was superior to that of non-enhanced 3D power Doppler ultrasound. The authors concluded that contrast-enhanced 3D power Doppler imaging might, more precisely, discriminate benign from malignant complex adnexal masses.

Methods for vascular sampling by three-dimensional power Doppler angiography in solid and cystic-solid adnexal masses were described by Alcazar and Prka in 2009, in a study which analyzed the difference in reproducibility of 3D-PD vascular sampling between manual and 5 ccm sphere sampling. 3D power Doppler angiography has been proposed as a method of predicting malignancy in adnexal masses. This new technique allows the objective assessment of tumor vascularisation by means of power Doppler signals. The rationale of the technique is based on the fact that malignant ovarian tumors have a higher microvascular density than do benign tumors. Vascularity Index (VI) is thought to reflect vascular density, FI is thought to reflect blood flow in those vessels.

“Vascular Sampling”—a terminus created by Alcazar—is based on the manual outlining of solid tumor areas using the VOCAL software (GE Medical Systems) to measure their vascularisation. In conclusion, both manual and 5 ccm sphere sampling of 3D-PD angiography data sets are reproducible methods.

Ultrasound screening—as stated before by several other studies—could be more effective when a morphology indexing system is used. This may be of value especially for less experienced sonographers. Ameye et al, conducted a multicenter study with 1573 patients forming four subgroups of adnexal masses to improve pattern recognition:
(1) unilocular cyst, (2) multilocular cyst, (3) tumor with at least one solid component but no papillation,(4) tumor with papillation. In each subgroup the associated likelihood of malignancy was calculated, using all possible combinations of variables ranging from demographic characteristics, gray scale findings, blood flow indices, tumor marker CA 125, family history of breast or/and ovarian cancer, to color score (no flow, minimal flow, moderate, strong flow). The authors concluded that the subgroup system with likelihood calculation may improve characterization of ovarian tumors by nonexperts in gynecological sonography.

Detection of Stage I Disease

Preliminary results of our team in Zagreb showed that 3D power Doppler ultrasound can enhance and facilitate morphologic and functional evaluation of an early stage ovarian cancer. A five-year retrospective analysis was performed on the data from 43 referred patients with suspected stage I ovarian cancer subsequently confirmed by histopathologist. All the patients were preoperatively evaluated by four complementary sonographic methods: 2D transvaginal gray-scale, 2D transvaginal color Doppler, 3D
ultrasound and 3D power Doppler, during the week prior to surgery. Our results clearly demonstrated the significant impact of 3D power Doppler imaging on the accurate detection of stage I ovarian cancer. By using combined 3D morphology and vascular score indexing, we reached diagnostic accuracy of 97.7% in preoperative sonographic assessment of the suspected lesions (Table 4). These findings justify implementation of 3D ultrasound with power Doppler facilities in ovarian cancer screening programs, especially as a secondary screening tool.

**ZAGREB OVARIAN CANCER SCREENING TRIAL**

Following our first attempt to screen for ovarian cancer, in January 2001 we initiated the new ovarian cancer screening trial at our department, based on new diagnostic tools now used routinely by us.

**SUBJECTS AND METHODS**

During a five-year period, approximately 10,000 asymptomatic postmenopausal women of 50 years and 25 years of age with a positive family history of ovarian and/or breast cancer in at least one primary or secondary relative were offered to participate in the trial. The screening algorithm is illustrated in Figure 1. Primary screening includes annual transvaginal ultrasound (TV US) and transvaginal color Doppler (TVCD) examination/scoring according to the sonographic and color Doppler criteria established previously from our team. Women with an abnormal first level screen underwent a repeat TV US and TVCD sonogram depending on morphologic appearance: in the case of simple ovarian cyst after 4-6 weeks, while if complex ovarian cyst persisted, within 2 weeks. In patients with a persistently abnormal screen, secondary screening will be considered necessary, including 3D, 3D power Doppler and contrast-enhanced 3D power Doppler ultrasound evaluation, with a serum CA 125 determination. For an examination/scoring, three-dimensional sonographic and power Doppler criteria established in our previous study were used. In the case of an abnormal second level screen, surgical removal of the tumor and pathological examination was recommended.

| Table 4: Diagnostic accuracy of four different techniques (2D transvaginal US, 2D transvaginal color Doppler, 3D US, and 3D power Doppler) in preoperative sonographic assessment of 43 patients with suspected stage I ovarian cancer. |
|---------------------------------|-----------------|-----------------|
| **Technique**                  | **Preoperatively** |                 |
|                                | **No. of detected cancers (%)** | **No. of missed cancers (%)** |
| 2D US                          | 30 (89.8)        | 13 (30.2)       |
| Combined 2D US and Doppler score | 37 (96.0)        | 6 (14.0)        |
| 3D US                          | 32 (74.4)        | 11 (25.6)       |
| Combined 3D US and Doppler score | 41 (96.3)        | 2 (4.7)         |
|                                | 42 (97.7)        | 1 (2.3)         |
ILLUSTRATIVE CASE NO. 1—MORE ACCURATE DIAGNOSIS OF OVARIAN CANCER

In an asymptomatic, 51-year-old postmenopausal patient, on her first annual screen at our department, complex ovarian tumor suspicious of an early stage ovarian cancer was detected. Asking the patient for family history, we found that her aunt and uncle (mother’s brother) died from colorectal cancer. In the first step, transvaginal gray scale ultrasound was performed, which revealed a complex cystic-solid tumor of the left ovary, measuring 4.5 cm in the largest diameter, with detectable several high-level echo foci within the solid component of the lesion (Fig. 2). According to our sonographic criteria, morphology score of 6 (volume > 10 cm³, solid area > 1 cm, and mixed/high-level echo pattern) was suggestive of ovarian malignancy. Another step in our primary screening represented transvaginal color Doppler analysis of tumoral blood flow within the solid part of the tumor. It revealed RI of 0.36 (Fig. 3A) to 0.40 (Fig. 3B) as the lowest values.

According to our color Doppler criteria for ovarian malignancy, this finding was indicative for a malignant ovarian lesion. Three-dimensional ultrasound scan, as a part of our secondary screening process, clearly depicted a hyperechoic area within the solid part of a complex ovarian tumor (Fig. 4). 3D ultrasound did not add any significant morphological findings in comparison to 2D transvaginal gray scale US, besides more precise volume calculation.

Fig. 2: Transvaginal ultrasound scan of a complex cystic-solid ovarian tumor in a 51-year-old postmenopausal patient. Note several high-level echo foci within the solid component of the lesion.

Fig. 3A and 3B: Further analysis of tumoral blood flow within the solid part of the tumor using transvaginal color Doppler ultrasound revealed RI of 0.36 (A) to 0.40 (B), suggestive of ovarian malignancy.

Fig. 4: The same patient as in Figures 2 and 3. Three-dimensional ultrasound scan of a hyperechoic areas within the solid part of a complex ovarian tumor.
However, the vascular pattern obtained by further analysis with 3D power Doppler imaging revealed single-vessel arrangement and regularly separated vessels within the solid part of the tumor (Fig. 5), indicative of a benign ovarian lesion. As a result, 3D US combined index score of 6, and especially data on tumor vessels architecture enabled us to presume benign character of the described complex ovarian tumor. Also, CA 125 serum level of 10.5 U/ml was in normal ranges. Unilateral adnexectomy was initially performed via laparotomy, and «ex tempore» biopsy of the left ovary reported benign cystic teratoma. This surgical procedure was considered adequate. Final pathology confirmed previous finding.

From the case described above, we will try to emphasize several outstanding details in the application of multimodal ovarian cancer screening:

1. False-positive findings on transvagal color Doppler analysis tended to involve non-neoplastic lesions that contained dilated vessels because of possible local metabolic imbalances caused by underlying inflammatory process or necrosis;
2. With the addition of 3D power Doppler (to study tumor vessels architecture) as a secondary screening tool, the specificity of a screening test could be significantly improved. This imaging modality might accurately discriminate benign from malignant complex ovarian lesions on the basis of qualitative analysis of tumoral microcirculation;
3. This improved diagnostic accuracy may promote improved patient care in terms of different surgical approaches to benign ovarian tumors (laparoscopy) and ovarian cancer (laparotomy, laparoscopy in the future for the early stage disease), therefore facilitating appropriate physician referral.

ILLUSTRATIVE CASE NO. 2—THE DETECTION OF STAGE I DISEASE

Here we present an illustrative case of successfully detected stage IA ovarian cancer in an asymptomatic, 57-year-old postmenopausal patient. She was well-educated and concerned about family history of cancer, because her mother and mother’s sister had breast cancer. Besides regular mammography and gynecological check-ups, patient decided to perform gynecological ultrasound in an outpatient clinic, for the first time in her life.

Transvaginal gray scale sonography, performed by her primary care gynecologist, revealed a complex cystic-solid tumor of the right ovary, measuring 8 cm in diameter, with detectable papillary protrusions and thick, irregular septa (Fig. 6). Regarding ovarian morphology indicative for malignancy, she was immediately directed to our department for further ultrasound evaluation. We confirmed previous TV US finding, and morphology score of 8 was highly suspicious for ovarian malignancy. Another step represented transvaginal color Doppler analysis of tumoral blood flow which revealed RI of 0.40 as the lowest value (Fig. 7). According to our color Doppler criteria, this finding was indicative for a malignant ovarian lesion.

The vascular pattern obtained by further analysis with 3D power Doppler imaging clearly depicted disorganized, randomly dispersed vessels with irregular branching in the papilla (Fig. 8) and solid parts (Fig. 9) of the tumor, strongly associated with ovarian malignancy.

As a result, 3D US combined index score of 12, using data on tumor vessels architecture enabled us to make a correct preoperative sonographic diagnosis of an early stage ovarian cancer. On the other hand, CA 125 serum level of 16.3 U/ml was in normal range, giving us a false negative impression of a benign ovarian tumor. Standard oncological surgical procedure was performed, and histopathology reported stage IA endometroid adenocarcinoma of the ovary.
ILLUSTRATIVE CASE NO. 3—THE DETECTION OF STAGE I DISEASE

A West-European lady, 51 years, came to the hospitals first-aid because of lower back pain since 5 weeks. Still regular menstruations, no children. Ultrasound showed a complex ovarian cyst on the right side, and she was referred to the primary care gynecologist. Vaginal examination revealed a fixed mass in the right small pelvis, retroparauterine. Transvaginal ultrasound showed a complex ovarian cyst on the right side, with intracystic fluid of low echogenecity, and intracystic proliferations, which had not been visible by transabdominal ultrasound (Fig. 10), max. diameter 18 cm, volume 256 ccm (Fig. 11).

In 3D color and power Doppler mode—TVS vascularisation of the papillary intracystic projections, with irregular branching, stenosis, microaneurysms, and lacunae (Fig. 12). Pulsed wave Doppler shows continuous flow of venous type (Fig. 13). Using combined 3D morphology and vascular score indexing, these sonographic findings were highly suspicious of ovarian melanoma (Figs 14A to D). Serum levels of CA 125 were not increased. MRI did not show any signs of regional or systemic metastasis. The patient was scheduled for laparoscopy/laparotomy with frozen section and bilateral ureter stenting. Laparoscopy showed us an immobile cystic ovarian tumor with smooth surface, of which only 1/5 was visible (Fig. 15). Under these circumstances we continued with laparotomy via midline incision. An immobile right ovarian tumor was released after spilling-free removal of the intracystic fluid (Fig. 14E). Frozen section diagnosis was malignant neoplasm with features of adenocarcinoma. Preliminary diagnosis was followed immediately by staging with hysterectomy, left adnexitomy, omentectomy, and para-aortic and iliac lymphonodectomy. The final histological diagnosis was clear cell carcinoma, staging pT1a. Focal endometriosis was found in both ovaries and the right Fallopian tube (Figs 16A to C).
Fig. 10: Ovarian Ca 1A transabdominal ultrasound. Interestingly, only the topographic analysis provides any information about the tumor, obtainable because of shadowing and limited penetration depth.

Fig. 11: Ovarian Ca 1A B-mode, TVS. Tumor volume 256 cm3, echogenic fluid, papillary intracystic projections.

Fig. 12: Ovarian Ca 1A 3D power Doppler. Now, in close range of the tumor, TVS can pick up randomly dispersed vascular signals in the tumor papilla.

Fig. 13: Ovarian Ca 1A, TVS in CD PW mode: continuous low-resistance flow in the tumor papilla.

Fig. 14A: 3D Surface rendered papillary protrusions into the cyst. Reduced transparency because of echogenicity (detritus) of fluid contents of the cyst.

Fig. 14B: 3D Surface rendering and magic cut through the basis of the papillary tumor areas, in an attempt to depict infiltrative lesions of the ovarian capsule.
The surprisingly good staging result, looking at a tumor volume of 256 ccm, demands explanations. Kurman et al. suggested a new model which divides ovarian cancer into 2 groups designated type I and type II. Type I tumors are slow growing, generally confined to the ovary at diagnosis and develop from well-established precursor lesions, so-called borderline tumors. Type I tumors include low-grade micropapillary serous carcinoma, mucinous, endometrioid, and clear cell carcinomas. They are genetically stable and are characterized by mutations in a number of different genes including KRAS, BRAF, PTEN, and beta-catenin. Type II tumors are rapidly growing, highly aggressive neoplasms that lack well-defined precursor lesions; most are advanced stage at, or soon after, their inception. These include high-grade serous carcinoma, malignant mixed mesodermal tumors (carcinosarcomas), and undifferentiated carcinomas. The type II tumors are characterized by mutation of TP53 and a high level of genetic instability. Screening tests that focus on stage I disease may detect low-grade type I.
For several decades, endometriosis has been suspected of playing a role in the etiology of ovarian cancer. Epidemiological evidence from large-cohort studies confirms endometriosis as an independent risk factor for ovarian cancer. Further circumstantial evidence for this link was found in the common risk factors for ovarian cancer and endometriosis. These risk factors influence retrograde menstruation and endometriosis in the same positive or negative way. Based on data in the literature, the prevalence of endometriosis in epithelial ovarian cancer has been calculated to be 4.5, 1.4, 35.9, and 19.0% for serous, mucinous, clear-cell and endometrioid ovarian carcinoma, respectively. The risk of malignant transformation in ovarian endometriosis was calculated at 2.5% but this might be an underestimate. In addition, some authors described atypical endometriosis in a spatial and chronological association with ovarian cancer. Finally, molecular studies have detected common alterations in endometriosis and ovarian cancer. These data suggest that some tumours, especially endometrioid and clear-cell carcinomas, can arise from endometriosis. Moreover, endometriosis-associated ovarian cancer represents a distinct clinical entity, with a more favorable biological behaviour, given a lower stage distribution and better survival than nonendometriosis-associated ovarian cancer.

**ILLUSTRATIVE CASE NO. 4—THE DETECTION OF STAGE 3 DISEASE**

A lady of Middle-East ethnicity, 48 years, with lower abdominal discomfort and bloated feeling in the abdomen since three months, came to see the primary care gynecologist for her annual examination. She had hypertension and diabetes mellitus type 2, was on metformin. Two children with normal vaginal deliveries. One sister suffered from breast cancer, with mastectomy. The patient had a normal gynecological check-up result one year before by a gynecologist, but no ultrasound had been done. Recently she noticed irregular menstruation.

Ultrasound showed bilateral complex adnexal masses of max. diameter of 7 cm, in color Doppler with randomly dispersed vascular pattern in the echogenic components of the mass (Figs 17 and 18).
Laparotomy was performed after magnetic resonance imaging (MRI). CA 125 preoperative 1404 U per ml, postoperative staging FIGO III. She had metastasis in omentum, para-aortic lymphnodes, and uterine infiltration. Cytology of peritoneal fluid (PF) was positive for cancer cells. Histology: high-grade serous-papillary carcinoma, moderately differentiated, of both ovaries. Remission after Carbo-Taxol chemotherapy.

What is important to stress from the previously described cases for ovarian cancer screening?

1. The 3D power Doppler qualitative analysis of tumor angiogenesis allows accurate detection of the earliest appearance of ovarian malignancy, i.e. stage IA ovarian cancer;
2. At the present time, higher equipment costs and more sophisticated operator skills make 3D ultrasound technology ideally available in clinical and university hospital settings as a secondary screening tool;
3. As published by Holbert, and noted in the case above, routine screening for ovarian cancer by standard 2D ultrasound modalities, in terms of primary screening, is a valuable addition to the yearly examination in outpatient clinics and private gynecology office settings;
4. Stage 1 detection of type 2 highly aggressive, fast growing ovarian neoplasma remains a challenge.

AIMS

Application of new 3D ultrasound technologies on patients with «positive» standard ultrasound tests represents an innovation compared with previous ovarian cancer screening trials. In this way, we were able to demonstrate for the first time that a secondary screening based on morphologic and vascular parameters assessed by 3D ultrasound, 3D power Doppler and contrast-enhanced 3D power Doppler may improve early detection of ovarian cancer and accuracy of ultrasound screening strategy in high-risk populations. Regarding this hypothesis, the primary end point of our screening trial was to improve the highest positive predictive value of 20% reached by multimodal screening, resulting in less than five operations for each ovarian cancer found as an excellent surgery to malignancy ratio.

CONCLUSION

Although a critical evaluation of the published screening trials leads to the conclusion that routine screening for ovarian cancer appears to be of advantage, many efforts continue to identify new screening modalities in high-risk populations. It seems that potential balance of benefits, harms and costs of screening may be more favorable in women with an inherited predisposition for developing of ovarian cancer. In such groups, compared with general population, fewer women need to be screened for each case detected, prevalence of the disease is markedly higher and the ratio of false positives to true positives is lower.

Because most of the ovarian cancers occur in general population, there has been growing interest in the possibility of screening for those with an increased risk, i.e. asymptomatic postmenopausal women. Two main strategies, multimodal and ultrasound based, have emerged, both with some limitations for implementation in a routine screening practice. For the first one, the great challenge is to improve the sensitivity of serum CA 125 as a primary screening tool. The risk of ovarian cancer algorithm (ROCA), an exponential model using data from several prior scans and testing for an exponential rise in the value of the marker, is likely to improve the sensitivity of CA 125 as the first line screening test. More promising ovarian tumor markers appear at the horizon.

In view of the persisting threat especially from ovarian type two cancer, it is comforting to know that 3D ultrasound imaging can emend the ability to differentiate benign from malignant masses, and can significantly increase specificity and positive predictive value (PPV) in ovarian cancer detection. Further analysis with 3D power Doppler (3D-PD) clearly depicts disorganized, randomly dispersed vessels with irregular branching in the solid part of the tumor, strongly associated with ovarian malignancy. 3D power Doppler imaging provides data on tumor vessel architecture for accurate preoperative diagnose of an early stage of an ovarian cancer.
Therefore, the problem of low PPV in 2D ultrasound-only strategies may be solved by introducing the new 3D ultrasound technology, used as a secondary screening procedure. The role of 3D ultrasound, 3D power Doppler and contrast-enhanced 3D power Doppler in early and accurate detection of ovarian was confirmed through the Zagreb Ovarian Cancer Screening Trial.

REFERENCES


Fishman DA, Cohen LS. Is transvaginal ultrasound effective for screening asymptomatic women for the detection of early-stage epithelial ovarian cancer? Gynecol Oncol 2000;77:347-49.


