

# Screening for Ovarian Cancer by Different Modes of Transvaginal Sonography

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## ABSTRACT

Studies indicate that 3D power Doppler imaging can improve the ability to differentiate benign from malignant ovarian masses, increasing significantly specificity and positive predictive value (PPV) in ovarian cancer detection. Therefore, the problem of low PPV in ultrasound-only strategies may be solved by introducing new 3D ultrasound technologies, used together in a secondary screening procedure. The possible role of 3D ultrasound and 3D power Doppler imaging in the early and accurate detection of ovarian cancer is under evaluation through Zagreb Ovarian Cancer Screening Trial.

**Keywords:** 3D power Doppler, Early detection, Malignant ovarian masses, Screening

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## INTRODUCTION

In developed countries, more women die annually from ovarian cancer than from all other gynecologic malignancies combined. For example, in the United States, approximately 25,580 new cases are diagnosed each year, and 16,090 of these women will die of the disease.<sup>1</sup> Symptoms usually do not become apparent until the tumor compresses or invades adjacent structures, ascites develops, or metastases becomes clinically evident. As a result, around 65% of women with ovarian cancer have advanced disease (Stage III/IV) at diagnosis with a 5-year survival rate of only 20 to 30%, compared with the 5-year survival of over 90% in patients with stage IA ovarian cancer, when the disease is confined to the ovary.<sup>2</sup> 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,<sup>3</sup> there is much enthusiasm for the development of effective screening methods/assays for the early detection of epithelial ovarian cancer.

## 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.<sup>4</sup> First, the anatomic location of the ovaries is not amenable to any direct inspection. Additionally, in contrast to cervical neoplasia, epithelial ovarian cancers lack any defined precursor lesion and have a poorly defined natural history. The time required for the localized disease to progress to disseminated disease is unclear; 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 specificity of 99.6% is required 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.<sup>5</sup> A specificity lower than this is likely to be unacceptable in this population, although may be acceptable to those with a positive family history of breast or ovarian cancer.

## ATTEMPTS TO SCREEN SOME LESSONS LEARNED

During the last decade, large prospective studies of screening for ovarian cancer have been performed.<sup>6</sup> Two distinct strategies have emerged, one based on ultrasound as the primary test, and the other involving the serum tumor marker CA 125 for primary screening with ultrasound as the secondary test (multimodal screening). Tables 1 and 2 summarize the prospective ovarian cancer screening studies in the general population.<sup>7-22</sup> If we exclude those which used transabdominal ultrasound, an abandoned screening strategy due to the unacceptably high rate of false-positive results, several important lessons can be learned for forthcoming trials.

As seen in 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

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

Study	Inclusion criteria	Screening strategy	No. of screened	No. of invasive epithelial ovarian cancers detected <sup>a</sup>	No. of positives screens	No. of positive screens/cancer detected <sup>b</sup>
<i>Ultrasound (US) approach</i>						
Grayscale US (Level 1 screen), then repeat grayscale US (Level 2 Screen)						
Nagell et al. <sup>7</sup>	Age > 50 years and postmenopausal or > 30 with positive family history	TVS Annual screens Mean 4 screens/women	14469	11 (6) 5 Stage	180	16,4
Hayashi et al. <sup>8</sup>	Age > 50 years	TVS	23451	3 (3)	258	<sup>c</sup>
Tabor et al. <sup>9</sup>	Aged 46–65 years	TVS	435	0	9	-
Campbell et al. <sup>10</sup>	Age > 45 years or with positive family history (4%)	TAS 3 screens at 18 monthly intervals	5479	2 (3) 2 Stage I	326	163
Goswamy et al. <sup>11</sup>	Age 39-78 Postmenopausal	TAS	1084	1 1 Stage I	not precised	-
Grayscale US and CDI (Level 1 screen)						
Vuento et al. <sup>12</sup>	Aged 56–61 years	TVS and CDI	1364	(1)	5	-
Kurjak et al. <sup>13</sup>	Aged 40–71 years 4 stage I	TVS and CDI	5013	4	38	9,5
Schulman et al. <sup>14</sup>	Age > 40 years or > 30 with positive family history	TVS and CDI	2117	1	18	18
Grayscale US (Level 1 screen) and other tests (Level 2 screen)						
Sato et al. <sup>15</sup>	Age > 30 years	TVS then tumour markers if TVS +, CT and MRI if all previous +	51550	16 (6) 12 Stage I	324	20,3
Parkes et al. <sup>16</sup>	Aged 50–64	TVS then CDI if TVS +	2953	1 1 Stage I	15	15
Holbert et al. <sup>17</sup>	Postmenopausal Aged 30–89 years	TVS then CA 125 if TVS +	478	1 1 Stage I	33 <sup>d</sup>	-
TOTAL <sup>e</sup>				37 (16) 23 Stage I	880	23,8

TAS = Transabdominal ultrasound; TVS = Transvaginal ultrasound; CDI = Color Doppler imaging

<sup>a</sup>The borderline/granulosa tumors detected are shown in parenthesis<sup>b</sup>Only invasive epithelial ovarian cancers included<sup>c</sup>Only 95 women consented to surgery and there are no follow-up details on the remaining<sup>d</sup>Only 11 of these women underwent surgery<sup>e</sup>Studies used TAS are excluded

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.

This article updates the status of ovarian cancer screening and addresses most relevant studies published during the last years. The developments that followed the review 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 the early and accurate detection of ovarian malignancy is discussed. Finally, we describe our new ovarian cancer screening trial, which started in January 2001.

## SCREENING TESTS

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

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

Study	Inclusion criteria	Screening strategy	No. of screened	No. of invasive epithelial ovarian cancers detected	No. of positive screens	No. of positive screens/cancer detected
<b>CA 125 only</b>						
Einhorn et al. <sup>18</sup>	Age >40 years	Serum CA 125	5550	6 2 Stage I	175	29.2
<b>Multimodal Approach</b>						
CA 125 (Level 1 Screen), Then Gray-scale US (Level 2 screen)						
Jacobs et al. <sup>19</sup>	Age >45 years Postmenopausal 3 annual screens	RCT Serum CA 125 TAS/TVS, if CA 125↑	10958	6 3 Stage I	29	4.8
Jacobs et al. <sup>20</sup>	Age >45 years Postmenopausal	Serum CA 125 TAS, if CA 125↑	22000	11 4 Stage I	41	3.7
Adonakis et al. <sup>21</sup>	Age >45 years	Serum CA 125 TVS, if CA 125↑	2000	1 (1) 1 Stage I	15	15
Grover et al. <sup>22</sup>	Age >40 years or with positive family history (3%)	Serum CA 125 TAS/TVS, if CA 125↑ 3 screens	2550	1	16	16
TOTAL <sup>a</sup>				19 (1) 8 Stage I	101	5.3

RCT = Randomised controlled trial

<sup>a</sup>Only multimodal approach studies included.

## 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.<sup>23</sup> Although CA 125 is elevated (>35 U/mL) in more than 80% of patients with epithelial ovarian cancer it is only 25% sensitive for early stage disease.<sup>24</sup> Indeed, its value as an initial screening tool is limited since picking up Stage III disease at an earlier time may not alter the outcome. To improve further the performance of CA 125 as a screening tool, an algorithm incorporating age, the rate of change of CA 125 and absolute levels to calculate an individual's risk of ovarian cancer has been described.<sup>25</sup> 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 is an integral part of the multimodal screening strategy adopted in the St Bartholomew's Hospital newest randomized control trial.<sup>26</sup>

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.<sup>27</sup> 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 M11). 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.<sup>28</sup>

Lysophosphatidic acid (LPA), a bioactive phospholipid with mitogenic and growth factor-like activities,<sup>29</sup> is a novel tumor marker that holds promise 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 Stages II, III and IV ovarian cancer, and all 14 patients with recurrent ovarian cancer.<sup>30</sup> 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—are essential for earlier detection and improved outcome for patients with ovarian cancer.<sup>31</sup>

## Transvaginal Ultrasound

Transvaginal ultrasound is used in most screening strategies either as the sole screening modality or as a secondary test after the 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 the further risk of ovarian cancer associated with various ultrasound findings.

Particular results of the largest ultrasound-based ovarian cancer screening project from the University of Kentucky might have a definitive impact on the design

of future ovarian cancer screening trials in the general population.<sup>32</sup> 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, are associated with minimal risk for ovarian cancer because there were no cases of ovarian carcinoma during a 5-year follow-up period.<sup>33</sup> 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. Recently, based on the data on 58,673 observations of ovarian volume, authors from Kentucky concluded that the upper limit of normal for ovarian volume is 20 cm<sup>3</sup> in premenopausal women and 10 cm<sup>3</sup> in postmenopausal women.<sup>34</sup> Such data are invaluable in determining optimal strategies for operative intervention in screening trials.

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.<sup>35</sup> In contrast, those with an elevated serum CA 125 level and abnormal ovarian morphology on ultrasound had a significantly increased cumulative risk of 24%. The use of ovarian morphology to interpret pelvic ultrasound may increase sensitivity, and use of complex ovarian morphology may increase the positive predictive value of a multimodal screening strategy.<sup>36</sup>

## 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 bulk 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 recent FIGO report,<sup>2</sup> the appearance of ovarian cancer is most common among women in early postmenopausal, an average age of 54 years. Law et al.<sup>37</sup> used national statistics to determine the number of years of life lost through deaths from 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 the loss of life peaked. The peak occurred in ovarian cancer during the age range 55 to 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 to 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 to 60%.<sup>38</sup> Various studies have put forward schemes for stratifying women into different risk categories of risk for breast and ovarian cancer by family history, genetic predisposition or both. Pharoah et al.<sup>39</sup> reviewed the relevance of family history in defining the target population for familial ovarian cancer screening, and propose 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.<sup>40</sup> 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 centres, members of breast cancer only families with an early onset of breast cancer.

## 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 most recent update from the 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.<sup>7</sup> 180 patients with persisting transvaginal abnormalities were subjected to surgical intervention. 17 primary ovarian cancers were detected of which 11 were epithelial ovarian cancers (EOC), three were granulosa cell tumors,



**Table 3:** Eligibility criteria for the UK National Familial Ovarian Cancer Screening Study<sup>39</sup>

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:

1	Two or more first degree relatives <sup>a</sup> with ovarian cancer.
2	One first degree relative with ovarian cancer and one first degree relative with breast cancer diagnosed under 50 years of age.
3	One first degree relative with ovarian cancer and two first or second degree relatives <sup>b</sup> with breast cancer diagnosed under 60 years of age.
4	An affected individual with one of the known ovarian cancer predisposing genes.
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.

<sup>a</sup>A first degree female relative is mother, sister or daughter.

<sup>b</sup>A second degree female relative is grandmother, granddaughter, aunt or niece.

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%, the 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 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, the 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 in future screening algorithms, consideration should be given to a screening interval of 6 months.

In the recently published Japanese ovarian cancer screening trial, 51,550 women aged 30 years or more attending for annual cervical screening underwent TV US screening for ovarian cancer.<sup>15</sup> 324 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 note that only 29.7% 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 group in screening for ovarian malignancy led by Jacobs recently reported the results of the first completed randomized trial of ovarian cancer screening.<sup>19</sup> This study randomized asymptomatic postmenopausal women aged 45 years or older to no screening (n = 10 977) or annual multimodal screening for 3 years (n = 10 958). In the screening group, 29 women with raised CA 125 values and abnormal ultrasound findings were referred for surgical investigation. All six 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.

## High-risk Population

For women with a known germline mutation or with a family history suggesting a significant possibility of a genetic predisposition to ovarian cancer, the appropriate screening strategy remains undefined. In recent studies, most authors advocate multimodality screening using TV US and serum CA 125 in patients who elect to delay or decline prophylactic oophorectomy. However, there is no consensus as to 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.<sup>41</sup> 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, one stage I EOC and 7 cases of primary peritoneal serous papillary carcinoma were diagnosed. Ultrasound abnormalities triggered surgical exploration in all three cases of the

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—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 the more reliable identification of 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.<sup>42,43</sup> While the addition of 3D power Doppler provides a new tool for measuring the quality of ovarian tumor angiogenesis,<sup>44</sup> improving accurate diagnosis of ovarian malignancies,<sup>45</sup> its clinical value for the early detection of ovarian carcinoma has yet to be determined.

### What does 3D Ultrasound Add?

In the pioneering work, Bonilla-Musoles et al.<sup>42</sup> 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.<sup>46-49</sup> A score greater than 4 caused suspicion of a malignant ovarian mass.<sup>49</sup> 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 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 diagnosis of ovarian cancer and possible detection of stage I disease.

### More Accurate Diagnosis of Ovarian Cancer

To determine whether three-dimensional power Doppler can improve the ability to differentiate benign from malignant ovarian masses, Kurjak et al.<sup>50</sup> 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 1 case of serous cystadenocarcinoma, while 3 benign lesions (dermoid cyst, ovarian fibroma, and ovarian cystadenofibroma) were considered false positive. In one case of cystadenofibroma, 3D power Doppler finding was 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 vascularity architecture had a sensitivity, specificity, and PPV of 100, 99.08, and 91.67% in detection of ovarian malignancy, respectively.

In the recently published study by Cohen et al.,<sup>51</sup> 71 women with a known complex pelvic mass were referred for a preoperative ultrasound evaluation with both two-dimensional grayscale and 3D power Doppler ultrasound. All the women underwent surgical exploration, and 14 had ovarian cancer. Two-dimensional grayscale 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. Despite 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, the authors stated, may promote improved patient care by separating complex benign masses from ovarian cancer, therefore

facilitating appropriate physician referral.

Kupesic and Kurjak very recently reported on the use of contrast-enhanced, 3D power Doppler ultrasound in the differentiation of benign and malignant adnexal lesions.<sup>52</sup> 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 nonenhanced 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 at 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 nonenhanced 3D power Doppler ultrasound. Authors concluded that contrast-enhanced 3D power Doppler imaging might more precisely discriminate benign from malignant complex adnexal masses.

### Detection of Stage I Disease

Preliminary results of our team showed that 3D power Doppler ultrasound can enhance and facilitate morphologic and functional evaluation of an early stage ovarian cancer.<sup>53</sup> A five-year retrospective analysis was performed on the data from 43 referred patients with suspected stage I ovarian cancer subsequently confirmed by a histopathologist. All the patients were preoperatively evaluated by four complementary sonographic methods: 2D transvaginal grayscale, 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 a diagnostic accuracy of 97, 7% in the preoperative sonographic assessment of the suspected lesions (Table 4). These findings justify the 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,<sup>13</sup> in January 2001 we initiated the new ovarian cancer screening trial at our Department, based on new

**Table 4:** Diagnostic accuracy of four different techniques [two-dimensional (2D) transvaginal ultrasound (US), 2D transvaginal color Doppler (TVCD), three-dimensional (3D) US, and 3D power Doppler (3D PD)] in preoperative sonographic assessment of 43 patients with suspected stage I ovarian cancer<sup>53</sup>

No. of technique	No. of detected cancers (%)	Missed cancers (%)
2D US	30 (69,8)	13 (30,2)
2D US/TVCD <sup>a</sup>	37 (86,0)	6 (14,0)
3D US	32 (74,4)	11 (25,6)
3D PD	41 (95,3)	2 (4,7)
3D US/3D PD <sup>b</sup>	42 (97,7)	1 (2,3)

<sup>a</sup>Combined 2D morphology and color Doppler score.

<sup>b</sup>Combined 3D morphology and power Doppler score.

diagnostic tools now used routinely by us.

### Subjects and Methods

During a five-year period, approximately 10,000 asymptomatic postmenopausal women  $\geq 50$  years and women  $\geq 25$  years of age with a positive family history of ovarian and/or breast cancer in at least one primary or secondary relative will be 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.<sup>54</sup> Women with an abnormal first level screen undergo a repeat TV US sonogram, with the addition of TVCD, depending on tumor morphologic appearance: in the case of the simple ovarian cyst for 4 to 6 weeks, while if complex ovarian cyst persists within 2 weeks. In patients with a persistently abnormal screen, the secondary screening will be considered necessary, including 3D ultrasound and 3D power Doppler imaging, with a serum CA 125 determination. For an examination/scoring, three-dimensional sonographic and power Doppler criteria established in our previous study are used.<sup>54</sup> In the case of an abnormal second level screen, surgical removal of the ovarian tumor and pathological examination is recommended.

### Illustrative Case

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

Transvaginal gray-scale sonography, performed



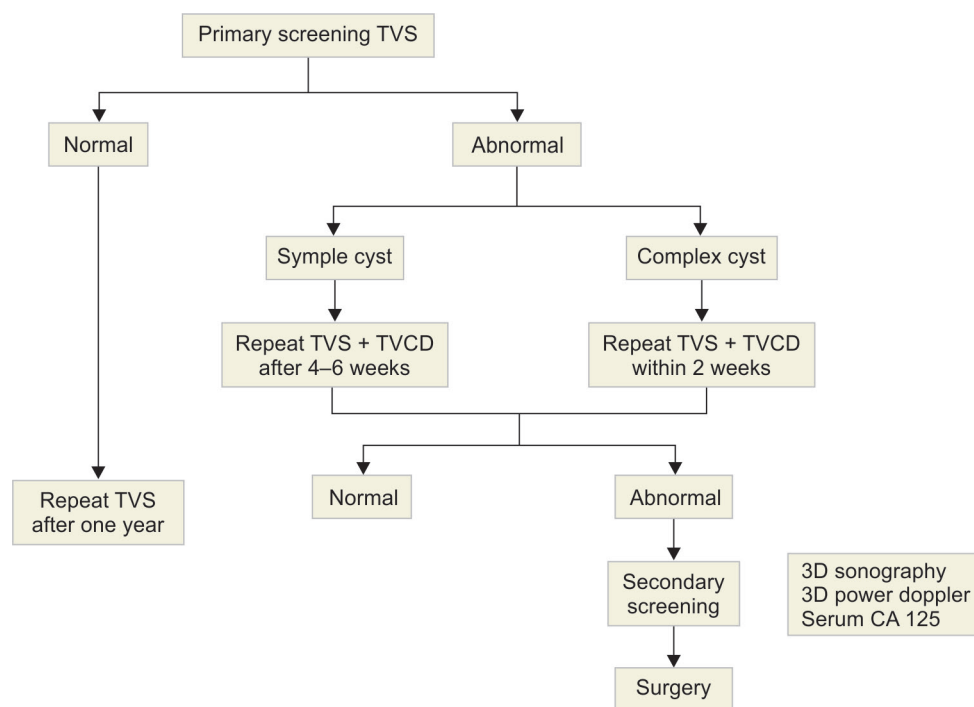


Fig. 1: Screening algorithm of the Zagreb ovarian cancer screening trial

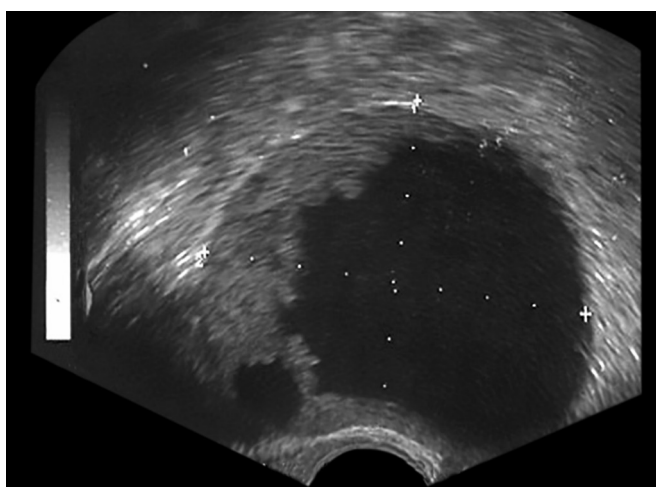


Fig. 2: Complex ovarian tumor in a 57-year-old postmenopausal patient, detected at our screening trial. B-mode showed noticeable solid component protruding into the cystic cavity of the tumor, measuring 8 cm in larger diameter. Note thick, irregular septum on the basis of the lesion

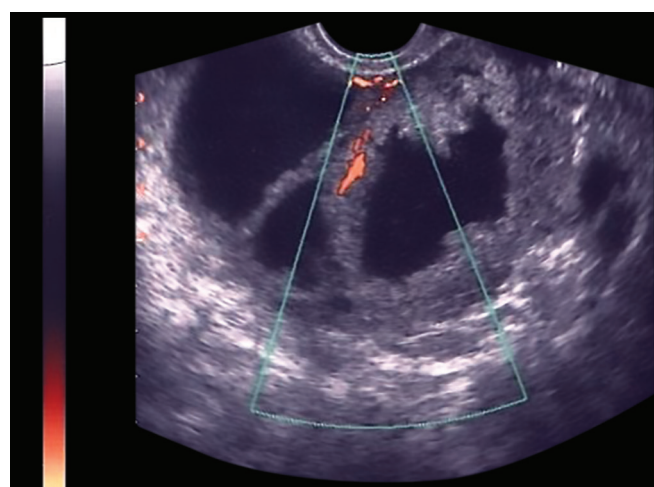


Fig. 3: Thick septa, solid component, and gross papillary projection on the basis of the lesion were obtained more clearly by B-mode in different section. Also, 2D power Doppler was switched on, showing highly vascularized septum

by her primary care gynecologist, revealed a complex cystic-solid tumor of the right ovary, measuring 8 cm in diameter, with noticeable solid component and thick, irregular septum (Fig. 2). Regarding ovarian morphology indicative for malignancy, she was immediately directed to our department for further ultrasound evaluation.

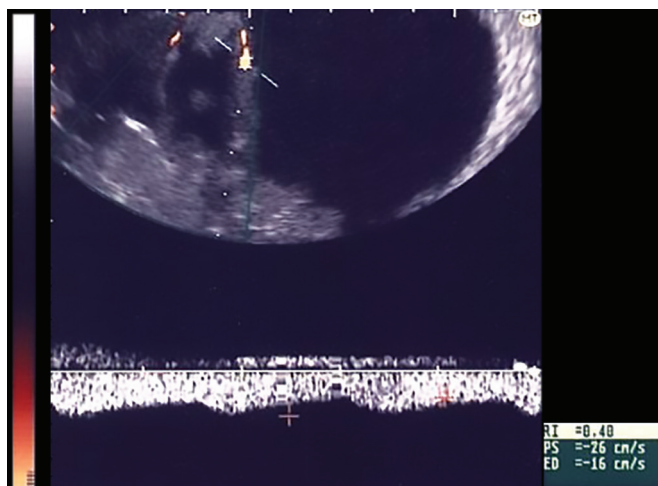
We confirmed previous TV US finding, and 2D power Doppler imaging showed highly vascularized zone within the septum (Fig. 3). Another step represented transvaginal color Doppler analysis of tumoral blood flow which revealed RI of 0, 40 as the lowest value

(Fig. 4). According to our color Doppler criteria, this finding was indicative for a malignant ovarian lesion.

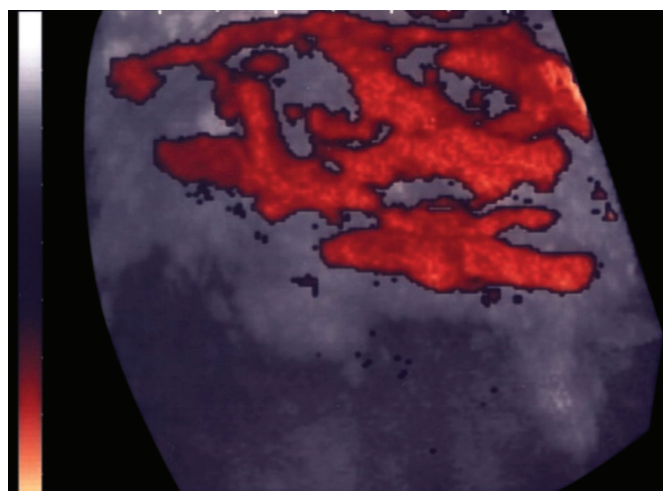
The vascular pattern obtained by further analysis with 3D power Doppler imaging depicted disorganized, randomly dispersed vessels with irregular branching in the solid part of the tumor (Fig. 5), strongly associated with ovarian malignancy.

As a result, 3D power Doppler data on tumor vessels architecture enabled us to make more accurately preoperative sonographic diagnosis of an early stage ovarian cancer. On the other hand, CA 125 serum level of 16.3 U/mL was





**Fig. 4:** Transvaginal color Doppler analysis of tumoral blood flow within the vascularized septum revealed RI of 0.40 as the lowest value. According to our 2D color Doppler criteria, this finding was indicative for ovarian malignancy



**Fig. 5:** 3D power Doppler imaging revealed malignant neovascularization within the solid part of the tumor, characterized by irregular course of the tumoral vessels and complicated branching. Histopathologic finding was stage IA ovarian endometrioid adenocarcinoma

in normal ranges, giving us a falsely negative impression of a benign ovarian tumor.

The standard oncological surgical procedure was performed, and histopathology reported Stage IA endometrioid adenocarcinoma of the ovary.

What is important to stress from the previously described case for ovarian cancer screening studies to come?

Three dimensional power Doppler qualitative analysis of tumor angiogenesis allows accurate detection of the earliest appearance of ovarian malignancy, i.e., stage IA ovarian cancer;

At present, 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.

As published by Holbert,<sup>55</sup> 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.

## Aims

Application of a new 3D ultrasound technologies on patients with positive standard ultrasound tests represents an innovation as compared with previous ovarian cancer screening trials. On this way, we plan to demonstrate for the first time that a secondary screening based on morphologic and vascular parameters assessed by 3D ultrasound and 3D power Doppler imaging may improve early detection of ovarian cancer and accuracy of ultrasound screening strategy in high-risk populations. Regarding this hypothesis, the primary endpoint of our screening trial will be 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 recently published screening trials has led to the conclusion that routine screening for ovarian cancer is not recommended at present, 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 the general population, fewer women need to be screened for each case detected, the prevalence of the disease is markedly higher, and the ratio of false-positives to true-positives is lower.

But, because the bulk of ovarian cancers occur in the general population, there has been growing interest in the possibility of screening for those at great risk, i.e., asymptomatic postmenopausal women. Two main strategies; multimodal and ultrasound-based have emerged, both still with some limitations for implementation in a routine screening practice. For the first one, the great challenge now 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 greatly sensitivity of CA 125 as a first-line screening test. On the other hand, ultrasound has favorable sensitivity in a primary screening, but the PPV of an ultrasound-based strategy is yet too low.

Recently published studies indicate that 3D power Doppler imaging can improve the ability to differentiate

benign from malignant ovarian masses, increasing significantly specificity and PPV in ovarian cancer detection. Therefore, the problem of low PPV in ultrasound-only strategies may be solved by introducing new 3D ultrasound technologies, used together in a secondary screening procedure. The possible role of 3D ultrasound and 3D power Doppler imaging in the early and accurate detection of ovarian cancer is currently under evaluation through Zagreb Ovarian Cancer Screening Trial.

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