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Three-dimensional Ultrasonography and Power Doppler in Ovarian Cancer Screening of Asymptomatic Peri- and Postmenopausal Women

Asim Kurjak, Matija Prka, José Manuel Bajo Arenas[1], Vladimir Šparac, Luis Tadeo Mercé[2], Ante Ćorušić[3], Mirjana Ivančić-Košuta[4]

Department of Obstetrics and Gynecology, Zagreb University School of Medicine, Holy Ghost General Hospital, Zagreb, Croatia; [1]Department of Obstetrics and Gynecology, Getafe University Hospital; [2]Department of Obstetrics and Gynecology, International Ruber Hospital, Madrid, Spain; [3]Department of Obstetrics and Gynecology, Zagreb University School of Medicine, Zagreb University Hospital Center, Zagreb, Croatia; and [4]Department of Kinesiological Anthropology and Methodology, Faculty of Kinesiology, University of Zagreb, Zagreb, Croatia

Aim To determine whether introducing three-dimensional (3D) ultrasonography with power Doppler facilities as a secondary screening test, preceded by annual transvaginal grayscale ultrasonography (TVUS) (followed by transvaginal color Doppler (TVCD) in selected cases) as a primary screening test for ovarian cancer improves the accuracy of ovarian cancer screening studies.

Methods Annual TVUS was performed on 3,201 peri- and postmenopausal asymptomatic women aged ≥50 years from March 1, 2001 to June 30, 2003. Cystic ovarian lesions in perimenopausal women were routinely reevaluated by TVUS and TVCD at 4-6 week intervals to avoid unnecessary surgical intervention for physiological cysts. Any multiloculated, complex or solid ovarian mass, as well as persistently cystic mass >5 cm in diameter, in which the echo architecture and/or blood flow pattern was not highly suggestive of a benign histology, was categorized malignant. In these cases, TVUS and TVCD findings were obtained in no more than 2 weeks and supplemented by secondary screening, including 3D ultrasonography, and 3D power Doppler, in combination with serum CA 125 determination. After detailed ultrasonographic examination, surgical removal of the tumor and pathohistological classification were completed.

Results Twenty-five patients (0.8%) with persisting ultrasonographic abnormalities after primary and secondary screening underwent surgery to remove the ovarian tumor. Five epithelial ovarian cancers were detected: 3 stage IA, 1 stage IB, and 1 stage IC. Three stage I patients had a palpable abnormality on clinical examination. Furthermore, in three patients with stage I disease, CA 125 serum value was elevated (≥35 U/mL). Three-dimensional ultrasonography and power Doppler, as well as TVUS findings were indicative of malignancy in all 5 patients with stage I ovarian cancer, whereas TVCD finding was false-negative in 2 patients with stage I disease. Screening test (primary+secondary screening) had the sensitivity of 100%, specificity of 99.4%, positive predictive value of 20%, and negative predictive value of 100%.

Conclusion Application of 3D ultrasonography and power Doppler imaging in patients with "positive" standard ultrasound tests (annual TVUS, followed by TVCD in selected cases) represents a novel approach for the early and accurate detection of ovarian cancer through screening.

Peri- and postmenopausal women aged ≥50 years have been considered at increased risk for ovarian malignancy (1). Although ovarian cancer is the second most common female reproductive cancer, preceded only by the cancer of the uterine corpus, more women die from ovarian cancer than from cervical and uterine corpus cancers combined.

According to the most recent data from 2002, incidence to mortality ratio in Croatia for ovarian cancer was 487/302, whereas this ratio for cervical and uterine corpus cancer was 366/98 and 492/67, respectively (2). In the United States, it has been estimated that ovarian cancer will be diagnosed in 22,220 women, and 16,210 women will die from this malignancy in 2005 (3). The principal reason for the poor outcomes is the advanced stage of the disease at diagnosis in 70-75% of cases and an overall 5-year survival of only 20-30%, compared with the 5-year survival of over 90% in patients with stage I ovarian cancer (4).

Since potentially curable ovarian cancers often do not produce any symptoms, efforts at early detection have focused on screening asymptomatic women at high risk of developing the disease. From the early 80-ies of the last century, large prospective studies of screening for ovarian cancer have been performed (5-13). Two distinct strategies have emerged, one based on transvaginal ultrasonography 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).

The data from a recent review (14) suggest that sequential multimodal screening has superior specificity and positive predictive value compared with strategies based on transvaginal ultrasonography alone. However, ultrasound as a first line test may offer greater sensitivity for early stage disease (56% cancers detected were stage I compared with 42% cancers detected by multimodal screening). Obviously, 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.

Latest technological advances, such as three-dimensional (3D) ultrasonography and 3D power Doppler, may have clinical utility in the early identification of abnormal ovarian vascularity and architecture (15). In recently published studies, 3D morphologic tumor evaluation combined with 3D power Doppler imaging has been proposed as a potential second-line ovarian cancer screening test, which could increase the positive predictive value of annual transvaginal gray-scale ultrasonography (TVUS) (16,17). According to our knowledge, this new approach in ovarian cancer screening has not yet been investigated.

In March 2001, Zagreb Ovarian Cancer Screening Trial was initiated in an attempt to assess whether introducing 3D ultrasonography with power Doppler facilities as a secondary screening test, preceded by annual TVUS (followed by transvaginal color Doppler (TVCD) in selected cases) as a primary screening test, will improve the accuracy of ovarian cancer screening studies based on ultrasound as a screening method. Present study summarizes the first results from our screening trial.

Subjects and Methods

Our prospective study, performed between March 1, 2001 and June 30, 2003 (28 months) included 3,201 women from the ovarian cancer screening trial.

Subjects

All asymptomatic women ≥50 years of age were eligible for the study. Postmenopause was defined as the absence of menstruation for a minimum of 12 months. Documented family history of ovarian and/or breast cancer in at least one first (mother, sister, or daughter) or second-degree (grandmother, grand-daughter, aunt, or niece) female relative was noted. Testing for BRCA1 and BRCA2 germ-line mutations was not performed routinely as a part of this trial. All study participants completed a questionnaire regarding past medical history and family history of cancer. After informed consent, participants underwent screening by a certified sonographer. Screening was provided at no cost to the participant.

Equipment

The ultrasound equipment used in the study were Aloka SSD 2000 (Aloka, Tokyo, Japan) and Voluson 530 or 730 (Kretztechnik, Zipf, Austria), all with 5 and 7 MHz transvaginal transducers. For serum CA 125 determination, we used hormonal analyzer (Abbott Diagnostics, Abbott Park, IL USA). The method of image acquisition and analysis for each of the four ultrasound techniques (TVUS, TVCD, 3D ultrasonography, and 3D power Doppler) is described in detail in our previous study (17).

Screening

Primary screening includes annual TVUS (Fig. 1). Women with a normal screen were scheduled to return in 12 months for a repeat screen. Cystic ovarian lesions in perimenopausal women were routinely re-evaluated by TVUS and TVCD at 4-6 week intervals to avoid unnecessary surgical intervention for physiological cysts (Fig. 1). Perimenopausal or postmenopausal women with thin-walled ovarian cysts <5 cm in diameter, without excrescences or septations, and unremarkable TVCD findings were followed with expectant management and were not considered operative candidates.

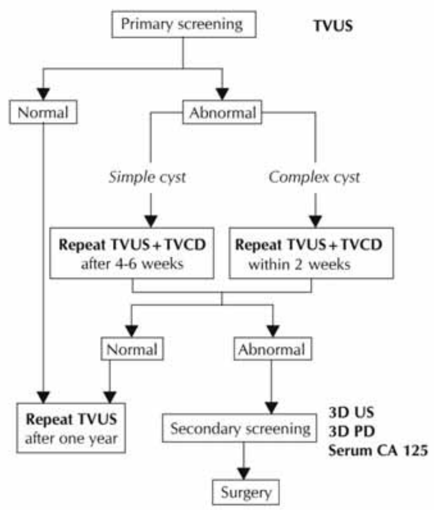

Figure 1. Screening algorithm of the Zagreb Ovarian Cancer Screening Trial. TVUS – transvaginal grayscale ultrasonography; TVCD – transvaginal color Doppler; 3D US – three-dimensional ultrasonography; 3D PD – three-dimensional power Doppler.

Diagnosis

Any multiloculated, complex, solid ovarian mass, or persistently cystic mass >5 cm in diameter, in which the echo architecture and/or blood flow pattern was not highly suggestive of a benign histology, was categorized malignant according to 2D morphological and Doppler criteria for ultrasonic diagnosis of the ovarian malignancy and related cut-off scores (Table 1). Cystic masses containing solid parts, excrescences, or thick or multiple septations were included within a complex category. The TVUSS and TVCD results were then supplemented by secondary screening within 2 weeks, including 3D ultrasonography, 3D power Doppler imaging, and serum CA 125 determination (Fig. 1). 3D morphological and Doppler criteria for ultrasonic diagnosis of the ovarian malignancy and related cut-off scores are shown in Table 1. CA 125 serum value did not influence the final decision for surgery, which was made before its determination (serum CA 125 ≥35 U/mL was considered abnormal).

Table 1. Two-dimensional (2D) and three-dimensional (3D) morphological and Doppler criteria and related scores for ultrasonic diagnosis of the ovarian malignancy

	Scores	
Criteria	2D morphology*	3D morphology†
Volume:		
premenopausal:		
<20 cm³	0	0
>20 cm³	2	2
postmenopausal:		
<10 cm³	0	0
>10 cm³	2	2
Cyst wall thickness/structure:		
smooth <3 mm	0	0
smooth >3 mm	1	1
papillae <3 mm	1	1
papillae >3 mm	2	2
Shadowing:		
present	0	0
absent	1	1
Septa:		
no septa	0	0
thin septa <3 mm	1	1
thick septa >3 mm	2	2
Solid parts:		
solid area <1 cm	1	1
solid area >1 cm	2	2
Echogenicity:		
sonolucency/low level echo	0	0
mixed/high level echo	2	2
Relationship with surrounding structures:		
normal	–	0
disturbed	–	1
	2D color Doppler*	3D power Doppler†
Tumoral blood flow:‡		
RI>0.42	0	–
RI≤0.42	2	–
Vessel architecture:		
linear	–	0
chaotic	–	2
Branching pattern:		
simple	–	0
complex	–	2

*Cut-off scores greater or equal to 4 for the morphology (2D morphology score) index and greater or equal to 6 for the combined (2D morphology and color Doppler score) index were associated with a high risk of ovarian malignancy (15).
†Cut-off scores greater or equal to 5 for the morphology (3D morphology score) index and greater or equal to 7 for the combined (3D morphology and power Doppler score) index were associated with a high risk of ovarian malignancy (15).
‡RI – resistance index.

Patients with persistently abnormal screens were operated on by the same surgical team (laparotomy or laparoscopy). After removal, ovarian tumors were photographed, measured in three dimensions, and examined for areas of morphologic abnormality. Then, each tumor was fixed, sectioned at 1.0 cm intervals, stained with hematoxylin and eosin, and examined microscopically. Tumors were classified histologically according to the World Health Organization (WHO) system (18) and staged according to the International Federation of Gynecology and Obstetrics (FIGO) system (4).

Outcome Measures

We took into account statistical definitions in ovarian cancer screening (9): true positive (TP), histology confirms primary epithelial ovarian cancer; false positive (FP), benign ovarian histology; true negative (TN), no evidence of disease 12 months following negative screen; and false negative (FN), ovarian cancer diagnosed within 12 months of negative screen. Using these data, sensitivity (TP/TP+FN), specificity (TN/TN+FP), positive predictive value (TP/TP+FP), and negative predictive value (TN/TN+FN) of the ovarian cancer screening test were calculated.

Statistical Analysis

Data were organized, counted, and analyzed using Microsoft Office Excel for Windows 2003 (Microsoft, Seattle, WA, USA).

Results

Screening participants were identified as 698 (21.8%) and 2,503 (78.2%) premenopausal and postmenopausal women, respectively. Their mean age (±standard deviation) was 58.4±7.2 (range, 50-85). The age distribution for the screened women is shown in Table 2. The mean parity was 1.7±0.9 (range 0-10), and 252 (7.9%) women were nulliparous. A family history of ovarian and/or breast cancer was documented in 341 (10.6%) of the screened women. Family history of cancer for these women regarding cancer origin included (ovarian, breast, and ovarian/breast cancer) (Table 2). Of the screened women, 427 (13.3%) were current users and 137 (4.3%) have used hormone replacement therapy.

The women enrolled in the trial (n=3,201) underwent a total of 4,202 scans (Table 3). One (for women who had undergone an ovariectomy) or both (for non-ovariectomized women) ovaries were visualized in 2,423 (57.7%) scans. Sonographically undetectable one or both ovaries (No. of scans=1,779; 42.3%) were considered normal for the purpose of this study.

In 25 patients (0.8%), primary and secondary screening revealed a pathological finding, and surgical removal of the ovarian lesion was performed in each of these patients. Patients underwent a total abdominal hysterectomy with bilateral salpingo-oophorectomy if there was a suspicion of ovarian malignancy or if they had an additional indication for hysterectomy other than the presence of a benign ovarian lesion (Table 4). Laparoscopic unilateral or bilateral salpingo-oophorectomy was the procedure of choice when there was no suspicion of ovarian malignancy. Clinical and pathohistological findings in 5 patients with primary epithelial ovarian cancer detected by annual screening are shown in Table 5. Stage distribution of these patients was classified as follows: 3 cases of stage IA; 1 case of stage IB; and 1 case of stage IC. Four stage I patients had ovarian tumors detected on the first screen, whereas in one stage I patient ovarian tumor was detected on the second screen. Three stage I patients had a palpable abnormality on pelvic examination and 2 of them had elevated CA 125 serum value. Elevated CA 125 serum value was recorded in 3 patients with

Table 2. Age distribution and family history of ovarian and/or breast cancer in screened women

Parameters	No. (%) of participants
Age (years):	
50-54	1,254 (39.2)
55-59	762 (23.8)
60-64	534 (16.7)
65-69	354 (11.0)
70-74	188 (5.9)
75-79	84 (2.6)
80+	25 (0.8)
total	3,201 (100.0)
Family history of cancer:	
ovarian	74 (2.3)
breast	259 (8.1)
ovarian and breast	8 (0.2)
total	341 (10.6)

Table 3. Distribution of the total number of scans experienced by 3,201 screened women

Total No. of scans	No. (%) of participants
One	2,452 (76.6)
Two	558 (17.4)
Three	143 (4.5)
Four	37 (1.2)
Five or more	11 (0.3)

Table 4. Surgical procedures in patients with persistently abnormal screens (n=25)

Surgical procedures	No. of patients
Laparoscopy:	
unilateral salpingo-oophorectomy	3
bilateral salpingo-oophorectomy	10
Laparotomy:	
hysterectomy, bilateral salpingo-oophorectomy	5
hysterectomy, bilateral salpingo-oophorectomy, and staging	7

Table 5. Clinical and pathohistological findings in patients with primary epithelial ovarian cancer detected by annual screening (n=5)

Patient	Age (years)	Family history of cancer	Screen No.	Pelvic examination	Serum CA 125 (U/mL)	Tumor size (cm)	Sonographic findings*: TVUS	TVCD (RI)	3D US and 3D PD	Histologic type	Tumor stage†
1	57	positive	1	palpable	16	8.7×7.0	complex	0.37	malignant	endometrioid	I A
2	69	negative	1	palpable	286	16.3×10.6	complex	0.43	malignant	endometrioid	I A
3	55	negative	1	palpable	99	10.1×8.9	complex	0.28	malignant	endometrioid	I A
4	60	negative	1	not palpable	117	5.6×3.4	complex	0.40	malignant	endometrioid	I B
5	62	positive	2	not palpable	17	4.9×3.2	complex	0.54	malignant	serous	I C

*Abbreviations: TVUS – transvaginal grayscale ultrasonography; TVCD – transvaginal color Doppler; 3D US – three-dimensional ultrasonography; 3D PD – three-dimensional power Doppler; RI – resistance index.
†Tumor staging according to Heintz et al (4).

stage I disease. Two of them had palpable adnexal masses, and 1 did not. Three-dimensional ultrasonography and power Doppler, as well as grayscale TVUS findings were indicative of malignancy in all 5 patients with stage I ovarian cancer, whereas color Doppler TVUS finding was false-negative in two patients with stage I disease. At the last follow-up, all patients diagnosed with ovarian malignancy were alive, doing well, and had no evidence of a recurrence.

The diagnoses of the remaining 20 patients with benign ovarian tumors who underwent surgery are shown in Table 6. The most common histologic diagnosis was simple ovarian cyst (35%), followed by cystic teratoma (15%), and cystadenofibroma (15%). One patient with granulosa cell tumor was false-positive for ovarian malignancy after the secondary screening.

Screening test (primary + secondary screening) had the sensitivity of 100%, specificity of 99.4%, positive predictive value of 20%, and negative predictive value of 100%.

Table 6. Pathohistological diagnosis of benign ovarian tumors (n=20)

Histological type	No. of patients
Pure benign ovarian tumors:	
simple ovarian cyst	7
cystic teratoma	3
cystadenofibroma	3
serous cystadenoma	2
mucinous cystadenoma	2
endometrioma	1
Benign ovarian tumors of unquestionable malignant potential:	
borderline serous cystadenoma	1
granulosa cell tumor	1

Discussion

Proposed Ovarian Cancer Screening Trial represents a novel approach for the early and accurate detection of ovarian cancer in asymptomatic women at high risk of developing the disease because of their age. Our preliminary results suggest that annual TVUS, followed by TVCD in selected cases, associated with secondary screening by using 3D ultrasonography and 3D power Doppler imaging has a potential to improve present positive predictive value of ultrasound-based ovarian cancer screening tests.

Because of the low incidence of ovarian cancer in clinical practice, reported to be approximately one case per 2,500 women per year, it has been estimated that a screening test with 100% sensitivity and 99.6% specificity is needed to achieve a positive predictive value of 10%, ie to limit the number of unnecessary surgical procedures to ten for each detected case of cancer (19). van Nagell et al in Kentucky, USA (9) and Sato et al in Hirosaki, Japan (10) have recently published results from ultrasound-based ovarian cancer screening studies. Screening test based on annual TVUS was associated with positive predictive values of 6.1% and 5.2% for detection of all primary epithelial ovarian cancers in Kentucky and Hirosaki trial, respectively (Table 7). In each of these trials, the positive predictive value of TVUS was obviously low. As correctly pointed out by van Nagell et al (9), whereas TVUS is relatively sensitive in identifying subtle abnormalities in ovarian volume and morphology, it does not distinguish reliably between benign and malignant ovarian tumors.

Folkman et al (20) first described the importance of angiogenesis for tumor growth. In our work, we included the hypothesis that ultrasonographic evaluation of tumor angiogenesis (21) might help us to improve differentiation between benign and malignant ovarian tumors detected in our screening trial. The study of several series has shown that angiogenesis might be detected with TVCD even when the carcinoma is confined within the ovarian capsule (22,23). On the other hand, parallel studies designed in favor of combined use of TVUS and TVCD as a primary screening test for ovarian cancer (Table 7), after initial promise, has not been widely accepted (7,8). Per-

Table 7. Largest prospective ovarian cancer screening studies in the general population primarily based on ultrasound imaging or serum CA 125 determination*

Study	Inclusion criteria	Screening strategy†	No. screened	No. of primary epithelial ovarian cancers detected‡	No. of surgical interventions	No. of surgical interventions/ cancer detected§	PPV‖ (%)
Ultrasound as a first-line test:							
Goswamy et al (5)	aged 39-78 years; postmenopausal	TAU	1,084	1 1 stage I	not detailed	–	–
Campbell et al (6)	age >45 years, or with positive family history (4%)	TAU; 3 screens at 18 monthly intervals	5,479	2 (3) 2 stage I	326	163	0.6
Kurjak et al (7)	aged 40-71 years	TVUS and TVCD	5,013	4 4 stage I	38	9.5	10.5
Schulman et al (8)	age >40 years, or >30 with positive family history	TVUS and TVCD	2,117	1	18	18	5.6
van Nagell et al (9)	age >50 years and postmenopausal, or >30 with positive family history	TVUS; annual screens; mean 4 screens/women	14,469	11 (6) 5 stage I 5 stage I	180	16.4	6.1
Sato et al (10)	age >30 years	TVUS, then tumor markers if TVUS+; CT and MRI if all previous +	51,550	17 (4) 12 stage I	324	20.3	5.2
Kurjak et al, 2005	age ≥50 years	TVUS, then TVCD if TVUS +; 3D US/3D PD and serum CA 125 if TVUS and/or TVCD+	3,201	5 5 stage I	25	5.0	20.0
Serum CA 125 as a first-line test:							
Einhorn et al (11)	age >40 years	serum CA 125	5,550	6 2 stage I	175	29.2	3.4
Jacobs et al (12)	age >45 years; postmenopausal	serum CA 125; TAU, if CA 125 ≥35 U/mL	22,000	11 4 stage I	41	3.7	26.8
Jacobs et al (13)	age >45 years; postmenopausal	RCT; serum CA 125; TAU/TVUS, if CA 125 ≥35 U/mL; 3 annual screens	10,958	6 3 stage I	29	4.8	20.7

*Adapted and modified from reference 14.
†Abbreviations: TAU – transabdominal ultrasonography; TVUS – transvaginal grayscale ultrasonography; TVCD – transvaginal color Doppler; 3D US – three-dimensional ultrasonography; 3D PD – three-dimensional power Doppler; CT – computed tomography; MRI – magnetic resonance imaging; RCT – randomized controlled trial; PPV – positive predictive value.
‡Borderline and granulosa cell tumors detected are shown in parenthesis.
§Only primary epithelial ovarian cancers included.
‖No. of primary epithelial ovarian cancers detected/No. of surgical interventions.

forming TVCD in every woman screened, even when normal ovarian morphology was established by TVUS, represented a cost-uneffective approach. For this reason, TVCD was dominantly used as a part of primary screening in our trial: 1) to reevaluate possible physiological cysts amongst perimenopausal women and, 2) to follow up, together with TVUS, peri- and postmenopausal women with simple ovarian cysts <5 cm in diameter. This was done in order to avoid unnecessary surgical interventions.

Morphological analysis of the blood vessel system by 3D power Doppler ultrasonography represents another approach to tumor diagnosis which, has not been extensively evaluated so far (24). Microscopically, ovarian tumor angiogenesis is highly heterogeneous and does not conform to normal vascular organization (25). In 2000, we presented the first results of 3D power Doppler imaging in the assessment of microcirculation anatomy of the ovarian lesions (26). One year later, Cohen et al (16) published a study on 71 women with a known complex pelvic mass who were referred for a preoperative ultrasound evaluation with both TVUS and 3D power Doppler. They correctly identified all 14 ovarian malignancies (2 FIGO stage I, 2 stage II, 7 stage III, and 3 metastatic colon) by both TVUS and 3D power Doppler imaging (sensitivity of 100%). Moreover, 3D power Doppler significantly improved the specificity, from 54 to 75%, as compared with TVUS.

Very recently, our group has published retrospective analysis on preoperative ultrasonographic assessment of 43 referred patients with suspected stage I ovarian cancer (17). Although the initial studies reported improved morphological evaluation of ovarian tumors by using 3D ultrasonography alone (27,28), in our analysis 3D ultrasonography reached unsatisfactory detection rate of 74.4%, whereas combined 3D ultrasonography and power Doppler imaging achieved the highest detection rate of 97.7% in preoperative ultrasonographic assessment of suspected ovarian lesions ($P\leq0.002$). Similarly, we proved that 3D ultrasonography with power Doppler facilities improve accurate detection of ovarian cancer, now in a selected population of asymptomatic women ≥50 years of age undergoing annual screening. Although 5 stage I ovarian cancers had abnormal morphology on TVUS, reevaluation with TVCD revealed false-negative finding in two patients with stage I disease. Only additional analysis with 3D ultrasonography and power Doppler helped us to distinguish reliably all five cases of stage I ovarian malignancy from the remaining 20 benign ovarian lesions.

From the clinical point of view, the fact that all 5 ovarian cancers detected in our screening trial were of stage I may result in a significant decrease in mortality from this disease. This seems to be an important finding, because Bell et al (29) have established that an increase in cancer detection at stage I from 25% to 50-75% might result in about 20-40% reduction in ovarian cancer mortality at five years. Moreover, our study reached high overall positive predictive value of 20%; in other words, five operations were undertaken for each detected case of primary epithelial ovarian cancer, significantly improving the surgery to malignancy ratio (Table 7). Regarding the remaining 20 benign ovarian masses detected and operated in our screening trial, minimally invasive surgical approach represented the main benefit of the accurate diagnosis.

Today, laparoscopy should be the initial step in the operative evaluation of the patients with ultrasonographic finding suggestive of benign ovarian tumors (30). With modern laparoscopic technology, the majority of those tumors can be removed intact and submitted for pathohistological evaluation. Thirteen out of 20 patients (65.0%) with benign ovarian tumors from our study were treated by laparoscopy and most of them were discharged within three days of surgery, which reduced medical costs. Patients with a frozen-section diagnosis of malignancy at laparoscopy can undergo immediate laparotomy with tumor debulking and surgical staging, if a gynecologic oncologist is on stand-by (31).

It is important to emphasize some limitations of our screening trial. Compliance by individual participants with the annual ovarian cancer screening was little bit lower than expected, partly because of intentional and prominent recruitment of the new screening participants at the beginning of the relatively short investigation period. Furthermore, we relied only on qualitative and descriptive 3D power Doppler criteria of ovarian tumor microcirculation anatomy, resulting in a subjective scoring system. Still, high equipment costs and sophisticated operator skills required by 3D ultrasound technology make its wider implementation in ovarian cancer screening studies difficult.

According to the recent American College of Obstetricians and Gynecologists Committee Opinion (32), data suggest that currently available ovarian cancer screening tests do not appear to be beneficial for screening low-risk asymptomatic women. Transvaginal ultrasonography has better sensitivity in a primary screening, but specificity and positive predictive value of an ultrasound-based strategy is yet too low. For this reason, concerns have been raised about the invasiveness of the surgery required to investigate positive screening results, the cost of screening, and the risk-benefit ratio.

Clearly, application of currently available 3D imaging modalities (3D ultrasonography and 3D power Doppler imaging) in patients with "positive" standard ultrasound tests (annual TVUS, followed by TVCD in selected cases) improves the accuracy of screening for ovarian cancer. In this way, we reached the positive predictive value of 20.0%, more than a three times higher result in than the positive predictive value of 6.1% from one of the largest ultrasound-based screening trials (9) and approached to the best up-to-date positive predictive value of 26.8%, success of a multimodal approach to ovarian cancer screening (12).

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Correspondence to:
Asim Kurjak
Department of Obstetrics and Gynecology
Zagreb University School of Medicine
Holy Ghost General Hospital
Sveti Duh 64
10000 Zagreb, Croatia
asim.kurjak@public.srce.hr