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## A new computer-aided diagnostic tool for non-invasive characterisation of malignant ovarian masses: results of a multicentre validation study

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**Abstract Objectives:** To prospectively assess an innovative computer-aided diagnostic technology that quantifies characteristic features of backscattered ultrasound and theoretically allows transvaginal sonography (TVS) to discriminate benign from malignant adnexal masses. **Methods:** Women ( $n=264$ ) scheduled for surgical removal of at least one ovary in five centres were included. Preoperative three-dimensional (3D)-TVS was performed and the voxel data were analysed by the new technology. The findings at 3D-

TVS, serum CA125 levels and the TVS-based diagnosis were compared with histology. Cancer was deemed present when invasive or borderline cancerous processes were observed histologically. **Results:** Among 375 removed ovaries, 141 cancers (83 adenocarcinomas, 24 borderline, 16 cases of carcinomatosis, nine of metastases and nine others) and 234 non-cancerous ovaries (107 normal, 127 benign tumours) were histologically diagnosed. The new computer-aided technology correctly identified 138/141 malignant lesions and 206/234 non-malignant tissues (98% sensitivity, 88% specificity). There were no false-negative results among the 47 FIGO stage I/II ovarian lesions. Standard TVS and CA125 had sensitivities/specificities of 94%/66% and 89%/75%, respectively. Combining standard TVS and the new technology in parallel significantly improved TVS specificity from 66% to 92% ( $p<0.0001$ ). **Conclusions:** Computer-aided quantification of backscattered ultrasound is a highly sensitive for the diagnosis of malignant ovarian masses.

**Keywords** Ovarian cancer diagnosis · Ultrasound · Ovarian HistoScanning · Tissue characterisation

### Introduction

Ovarian cancer is the fourth most common cancer in women, with annual incidence rates ranging between 8.5

and 21.5 per 100,000 women in European countries [1]. The International Agency for Research on Cancer estimated that, in 2002, there were 204,499 ovarian cancer patients and 124,860 ovarian cancer deaths worldwide [1].

In Europe, the average 5-year survival rate of ovarian cancer patients is around 40% [2]. The high case-fatality rate has largely been attributed to the fact that most ovarian cancers are at an advanced stage ( $\geq$ III) when diagnosed. Stage I cancer carries a survival rate exceeding 90%. Hence, there is a consensus that detection at early stages will lead to less morbidity and mortality. That is why bimanual pelvic examination associated with transvaginal sonography (TVS) is widely prescribed for women with any kind of pelvic symptoms or as part of a routine gynaecological examination. Although surgical management may be appropriate whether or not the mass is malignant, when a mass is detected in symptomatic women, the main reason to discriminate preoperatively between benign and malignant lesions is to facilitate referral to and management by clinicians who have specialised training and experience in managing ovarian malignancy, with improved outcomes [3]. In asymptomatic women, discriminating benign from malignant disease is also important to ensure appropriate management in the setting of malignancy and to avoid unnecessary diagnostic procedures, including surgery, when the lesion is not malignant and is not likely to undergo malignant transformation.

Combining morphology and Doppler TVS, the most common imaging technique for the discrimination of benign from malignant adnexal masses, achieves pooled sensitivity and specificity of 86% and 91% [4]. Many attempts have been made to improve this performance. Measurement of serum CA125, magnetic resonance imaging (MRI), computed tomography (CT) and positron-emission tomography (PET) using fluorodeoxyglucose were proposed [4–9]. MRI appeared to have similar sensitivity and slightly better specificity than Doppler TVS [6, 7, 9] but is more expensive and less available while CA125, CT and PET have poorer diagnostic performance than MRI or Doppler TVS [4]. Different risk-of-malignancy indexes, combining menopausal status, CA125 and TVS, were also proposed but, in validation studies, they did not improve performance above that of Doppler TVS alone [10–14].

The aim of this study was to prospectively assess a new way of increasing the ability of TVS to discriminate benign from malignant adnexal masses using a concept radically different from all tissue characterisation technologies proposed so far: Ovarian HistoScanning (OVHS, Advanced Medical Diagnostics, Waterloo, Belgium), which quantifies changes induced by malignant tissues in backscattered ultrasound waves when applied to voxel data generated during TVS.

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## Patients and methods

### Ovarian HistoScanning (OVHS)

Cancerous processes are characterised by various structural changes in tissue texture, e.g. disorganisation,

anisocytosis and anisonucleosis, which result in measurable physical changes of the reflected ultrasound waves, like energy loss, erratic spatial distribution of energy and increased entropy. The tissue characterisation algorithms of HistoScanning are based on mathematical methods that are trained to quantify such changes in the backscattered waves induced by cancerous tissue ([www.histoscanning.com](http://www.histoscanning.com)). The selection of the appropriate characterisation algorithms for a specific organ and their training are empirical processes that were previously tested on prostate cancers [15, 16]. For OVHS, three different characterisation algorithms were selected and trained during clinical development studies in 2001–02 on 98 ovaries from 78 patients aged 17–86 years (unpublished data from Advanced Medical Diagnostics) to discriminate normal from cancerous tissues. Borderline ovarian tumours exhibiting physical and structural changes comparable to ovarian cancer, without an invasive component and that could not be distinguished from invasive cancer by HistoScanning, were classified with ovarian cancers.

### Patients

Patients were recruited in five centres: University Hospital La Pitié-Salpêtrière, Paris, France; Karolinska Hospital, Stockholm, Sweden; European Institute of Oncology, Milan, Italy; Hospital La Charité, Berlin, Germany, and in the Rabin Medical Centre, Petah Tikva, Israel. Study protocol and procedures conformed with the Helsinki Declaration of Human Rights. The study protocol and the written information communicated to patients were approved by the Ethics Committees of all participating institutions provided that the study design was developed to avoid any interference of OVHS analysis with usual patient management.

All women aged at least 18 years who were scheduled for surgical removal of one or two ovaries because of the presence of an adnexal mass or as part of a prophylactic oophorectomy or hysterectomy with oophorectomy for a uterine abnormality (fibroid tumour, endometrial cancer) and who had given their written informed consent were prospectively included in this study. To exclude ultrasound data from ovaries that might have been altered, patients were not included if they had a history of ovarian cancer, previous pelvic surgery, or chemotherapy for breast or ovarian cancer.

### TVS and OVHS analyses

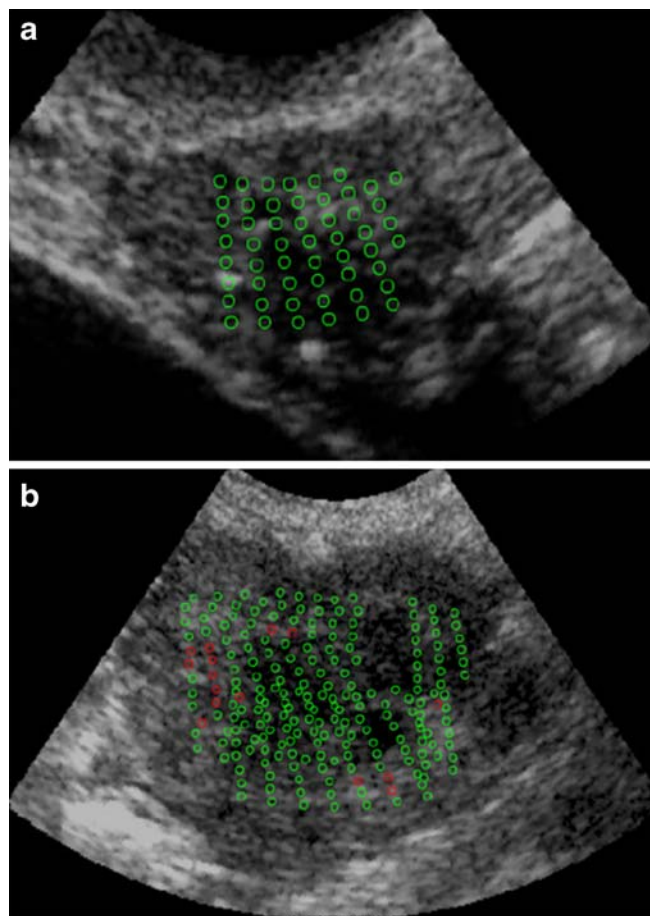
The day before surgery, all eligible women underwent TVS, performed by a gynaecologist or a radiologist with more than 10 years' experience using, in all participating institutions, a Voluson 730 Expert (GE Healthcare, Waukesha, Wis.) equipped with a 5- to 9-MHz real-time

four-dimensional (4D) endocavity transducer (RIC5–9; GE Healthcare). The examination started with 2D-TVS in which both ovaries and/or adnexal masses were identified. Then the operator performed, according to local practice, combined B-mode and Doppler real-time analyses. Neither B-mode morphological scoring systems [17–21] nor Doppler quantitative analysis [22, 23] was used to evaluate the ovaries. All study investigators performed a simple descriptive assessment of the presence or absence of arterial vessels, septa, unilocular or multilocular cysts within the mass, following the previously published guidelines [24–28] for ultrasound classification of ovaries. Based on that descriptive analysis alone, investigators were asked to classify each ovary seen as positive (malignant) or negative (benign) for malignancy.

Afterwards, 3D-TVS was performed to capture in Dicom mode all structures previously investigated during 2D-TVS of both ovaries. In the case of very large masses, several 3D acquisitions were obtained to cover the tumour. A special standardised protocol for 3D-TVS was followed in all participating centres: the dynamic control was set at 9, the resolution was set to maximum and the overall gain was limited to a range of  $-8 \text{ dB} \leq \text{gain} < -4 \text{ dB}$ . Ultrasound data for each patient were rendered anonymous and saved on a CD-ROM that was sent to the study coordinator, who collected data from all the participating centres.

OVHS analysis was performed secondarily at Advanced Medical Diagnostics (Waterloo, Belgium) without knowledge of the patient's TVS report, medical history, surgery outcomes or histology. Because the analysis was not performed in the presence of the sonographers who acquired the 3D-TVS data, they were asked, before sending the data, to delineate a region of interest (ROI) on the 2D image that corresponded to the mid-frame of the volume acquired and thus indicate the volume on which the OVHS analysis should be performed. At Advanced Medical Diagnostics, an independent gynaecologist, expert in diagnostic TVS, matched the annotated 2D images with the structure depicted by the 3D-TVS data and determined the extent of the volume to be analysed. The three characterisation algorithms were successively applied to overlapping units of  $20 \times 20$  voxels of ultrasound data equivalent to tissue volumes ranging from  $0.6$  to  $1.6 \text{ mm}^3$ , depending on the size of the field of view used. Threshold levels, predefined in preliminary development studies, below which the presence of cancer was unlikely, were applied to each characterisation algorithm. These results given by each algorithm were combined to give 0 (cancer unlikely) or 1 (cancer likely) probability of cancer for each elementary unit of  $20 \times 20$  pixels.

The OVHS report consisted of coloured circles superimposed on the 2D-ultrasound video image (Fig. 1). Each coloured circle represents the analysis result obtained in each elementary volume unit. When the circle is *green*, this elementary unit was considered non-malignant. When the



**Fig. 1a, b** OVHS analysis. The *circles* superimposed on the 2D ultrasound video image represent the results obtained for each elementary volume unit. *Green circles* are indicative of tissue volumes that do not pass the predefined threshold for positivity, while the *red circles* are indicative of tissue volumes that pass this threshold. **a** Based on OVHS, the ovary was considered negative for cancer, while the ovary in **b** was considered positive

circle is *red*, the elementary unit was considered malignant. Based on unpublished experience, *red circles* were generated only when at least  $\sim 100 \text{ mm}^3$  of consecutive volume units were positive. The participating centres did not have knowledge of the OVHS results, thereby avoiding any possible interference of the study with clinical practice, as requested by the Ethics Committees.

### Histology

Every removed ovary was subjected to histological examination by the pathology department of each centre. Conclusions and FIGO stages established by each centre were considered the final diagnoses, and used for statistical analysis. No centralised second reading was performed.

**Table 1** Patient characteristics

Characteristic	Value
Total number of patients	264
Median age (range)	57 (26–86)
Menopausal (yes/no)	190/74
CA125 <sup>a</sup> ( $\geq 35$ / $< 35$ )	110/94
Reason for surgery	
Symptomatic adnexal mass	72
Asymptomatic adnexal mass discovered at gynaecological examination/TVS	55
Ovaries removed during hysterectomy	91
Prophylactic oophorectomy	26
Other or missing data	20

<sup>a</sup>Performed according to local practice

### Statistical analysis

OVHS analysis results, serum CA125 levels determined according to local practice and the TVS-based diagnosis

made by the radiologist or gynaecologist were compared with histological findings using a chi-squared test. The specimen was considered positive for malignancy when a borderline ovarian tumour or an invasive cancerous process was observed histologically.

### Results

A total of 375 ovaries, were removed from 264 women eligible for the study. Patient characteristics are reported in Table 1. Pathologists diagnosed 141 (37.6%) cancers and borderline ovarian tumours, 127 benign lesions and 107 normal ovaries (Table 2). Ultrasonographers' opinions were available for 359 ovaries, serum CA125 levels for 273 and both for 267. OVHS alone correctly identified 138/141 malignant lesions, yielding 98% sensitivity, while TVS alone had a sensitivity of 94% (not significant) and CA125, using a threshold of 35 U/ml, a significantly lower sensitivity of 88% ( $p=0.005$ ) (Table 3). OVHS accurately classified all FIGO stage I/II invasive ovarian cancers as positive.

Among the eight TVS false-negatives, seven were OVHS positive (Fig. 2). On the other hand, OVHS had

**Table 2** Histology results

Histology	TVS ( $n=359$ )		CA125 ( $n=273$ )			OVHS ( $n=375$ )			
	<i>n</i>	Potentially malignant	Probably benign	<i>n</i>	$\geq 35$ U/ml	$< 35$ U/ml	<i>n</i>	Positive	Negative
Normal ovaries	104	8	96	50	10	40	107	4	103
Benign ovarian lesion	119	68	51	90	21	69	127	24	103
Ovarian cyst	38	18	20	25	5	20	40	2	38
Corpus albicans	17	3	14	9	1	8	18	0	18
Corpus luteum	8	3	5	5	3	2	8	3	5
Cystadenoma	16	13	3	17	1	16	18	3	15
Endometriosis	11	7	4	9	5	4	11	3	8
Cystadenofibroma	8	8	0	9	3	6	9	3	6
Dermoid	1	1	0	0	0	0	1	1	0
Teratoma	7	6	1	2	1	1	5	1	4
Brenner tumour	5	4	1	5	0	5	5	3	2
Thecoma	3	2	1	2	1	1	5	1	4
Malignant lesion	136	128	8	133	116	17	141	138	3
Invasive ovarian cancer	82	78	4	80	70	10	83	82	1
FIGO stage I	16	16	0	16	11	5	16	16	0
FIGO stage II	12	11	1	12	10	2	12	12	0
FIGO stage III/IV	54	51	3	52	49	3	55	54	1
Borderline ovarian cancer	24	23	1	24	17	7	24	23	1
Ovarian metastasis <sup>a</sup>	9	7	2	7	7	0	9	8	1
Peritoneal carcinomatosis	13	13	0	14	14	0	16	16	0
Cancer of organ invading the pelvis <sup>b</sup>	8	7	1	8	8	0	9	9	0

<sup>a</sup>One colon cancer, one cutaneous melanoma

<sup>b</sup>Cancers of the Fallopian tube

**Table 3** Results of the different tests. Combinations of two or three tests were considered positive when all results were positive or negative when at least one result was negative (*FP* false-positive, *TN* true-negative, *TP* true-positive)

Procedures	Total	TP	TN	FP	Sensitivity	Specificity
Overall results						
TVS	359	128	147	76	0.94	0.66
CA125	273	116	107	35	0.88	0.75
OVHS	375	138	206	28	0.98	0.88 <sup>a</sup>
TVS + CA125	261	106	117	17	0.83	0.87 <sup>a</sup>
TVS + OVHS	359	125	205	18	0.92	0.92 <sup>a</sup>
TVS + CA 125 + OVHS	361	103	129	5	0.81	0.96 <sup>a</sup>
Abnormal ovaries (benign or malignant lesion)						
TVS	255	128	51	68	0.94	0.43
CA125	216	116	64	21	0.86	0.75
OVHS	268	137	103	24	0.97	0.81 <sup>a</sup>
TVS + CA125	206	106	65	14	0.83	0.82 <sup>a</sup>
TVS + OVHS	255	125	102	17	0.92	0.86 <sup>a</sup>
TVS + CA 125 + OVHS	206	103	75	4	0.81	0.95 <sup>a</sup>
Ovaries TVS positive						
TVS	204	128		76	0.63	
CA125	184	106	47	17	0.86 <sup>b</sup>	
OVHS	204	125	58	18	0.87 <sup>b</sup>	
TVS + CA125	184	106	47	17	0.86 <sup>b</sup>	
TVS + OVHS	204	125	58	18	0.87 <sup>b</sup>	
TVS + CA 125 + OVHS	184	103	59	5	0.95 <sup>b</sup>	

<sup>a</sup>Values significantly higher than for TVS or CA125 alone

<sup>b</sup>Values significantly higher than for TVS alone

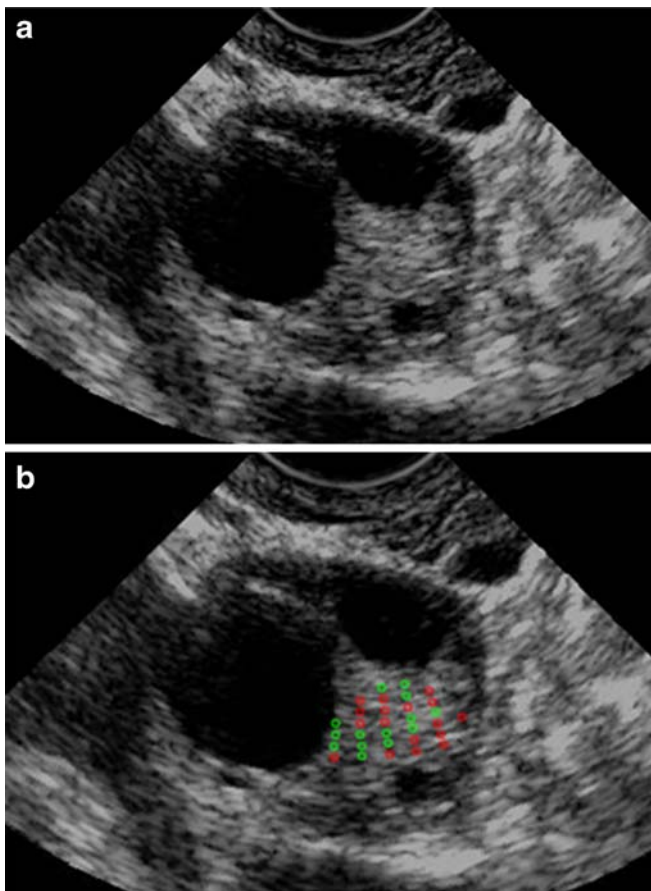
three false-negatives: the first concerned a 45-year-old woman with ovarian cancer  $\geq 100$  mm in diameter, classified FIGO IIIC; the second was an 18-mm breast cancer-related ovarian metastasis. These two ovaries were considered TVS-positive. The third concerned a 53-year-old patient with bilateral adenofibroma with borderline characteristics. The right ovary was classified OVHS-positive and the left ovary was OVHS-negative, and both were considered TVS-negative. The pathology report for the left ovary was “cystadenofibroma with microscopic foci of low malignant potential (borderline)”. OVHS alone correctly identified 206/234 non-malignant ovaries, yielding 88% specificity, while TVS and CA125 specificities were significantly lower at 66% and 75% ( $p < 0.0001$  and  $p = 0.01$ , respectively) (Table 3). OVHS specificity remained high (81%) when only abnormal ovaries (with benign or malignant lesions) were considered.

When TVS and OVHS were combined, the sensitivity for the subgroup of patients for whom both results were available and positive was comparable with the sensitivity of TVS alone: 92% versus 94% (Table 4), but the specificity was significantly improved: 92% versus 66% ( $p < 0.001$ ). Moreover, when comparing TVS + OVHS with TVS + CA125 for the respective subgroups (Table 4),

sensitivity was significantly improved ( $p = 0.01$ ) for comparable specificity. These results reflect the significantly fewer false-positive results obtained by the combination of OVHS and TVS compared with TVS alone. Indeed, for the subgroup of 119 benign lesions for which both TVS and OVHS data were available, false-positive results declined from 57% to 14% ( $p < 0.0001$ ). Among the 104 normal ovaries, OVHS adjunction did not significantly lower the TVS alone false-positive rate respectively, 3.7% versus 7.7%, while only four OVHS false-positives were recorded. On the other hand, among the ovaries considered potentially malignant with TVS, 37% were misclassified as false-negatives with TVS used alone. Combining TVS with CA125 or OVHS significantly decreased the false-positive rates to 9.2% and 8.8% respectively ( $p < 0.001$ ), while combining CA125 and OVHS and TVS yielded a false-positive rate of 2.7%.

## Discussion

Ovarian masses are common among women of all ages. Thus, it is very important to discriminate preoperatively between benign and malignant lesions to optimise the



**Fig. 2** **a** An example of an ovary considered to be normal with TVS. **b** The same TVS false-negative ovary with OVHS-detected foci of malignancy. The presence of an adenocarcinoma was confirmed histologically

management of ovarian cancer and avoid unnecessary diagnostic procedures. Ovarian masses are mainly discovered or first explored with TVS. The previously estimated TVS sensitivity was 86% [95% confidence interval (CI): 82–88%] from pooled sensitivities reported in 53 studies using a random effects model [4]. A limiting feature of TVS is its high rate of false-positive test results, which was estimated in the same studies to be around 17% (95% CI: 24–12%). Many attempts were made to improve the sensitivity and specificity of TVS, by using morpho-

logical scoring systems [17–21] or by combining morphological assessment with Doppler quantitative analysis [22, 23], but those approaches only slightly improved sensitivity to 89% (95% CI: 81–93%) and specificity to 0.91% (0.80–0.96%) (pooled data from Myers et al. [4]). Another approach to improving TVS performance was proposed using an expert system [29] and artificial neural networks [12, 30]. However, both techniques are based on data manually provided by the physician and, like the scoring systems, they are all based on subjective evaluations made by the operator. Until now, the principal attempts to automatically analyse ovarian ultrasound images mostly concerned the automatic segmentation of ovarian follicles [31–33] and only one paper focused on the automatic distinction between normal and abnormal ovarian regions [34]. Zimmer et al. [34] proposed an automatic analysis of the US images based on quantification of grey-level variations (mean, standard deviation, slope, etc.). Classification obtained with that software yielded a success rate of 80–90% for cysts but only 70% for tumours containing solid portions.

Herein, we evaluated an automatic scoring system, HistoScanning, which is based on the quantification of tissue disorganisation induced by malignant processes in backscattered ultrasound waves before image processing. HistoScanning was developed to be applied to digitally received radio frequency (RF) ultrasound signals which were backscattered from an imaging volume before processing by the built-in image production algorithms of the ultrasound machine that generates the video display. In that respect, HistoScanning is not an image-enhancement or -processing tool. In our study, however, because the manufacturer of the ultrasound machine used blocked our access to RF data, HistoScanning was applied to specifically calibrated and standardised voxel data that represent an almost linear depiction of the backscattered 3D raw data, thereby yielding homogeneous results obtained from the different centres. This technology is potentially promising either in improving the identification of cancers or to help characterise focal abnormalities in many fields in which ultrasound is widely used, such as breast, thyroid, prostate or ovary imaging. HistoScanning has previously demonstrated a high performance in identifying prostate cancer foci  $>0.50 \text{ mm}^3$  with 100% sensitivity and 82% specificity during presurgical trans-

**Table 4** Comparison of the different tests. Combinations of two or three tests were considered positive when all results were positive or negative when at least one result was negative

Test 1	Test 2	Sensitivity			Specificity		
		Test 1	Test 2	<i>p</i> value	Test 1	Test 2	<i>p</i> value
TVS	TVS+OVHS	0.94	0.92	0.08	0.66	0.92	<0.001
TVS +CA125	TVS + OVHS	0.83	0.92	0.01	0.87	0.9	0.37
TVS + CA 125	TVS + CA125+OVHS	0.83	0.81	0.08	0.87	0.96	<0.001

rectal sonography in 29 men [15, 16]. This technology has to be adjusted specifically to each targeted organ. For ovaries, the core of the system, which is specifically called OVHS, consists of three specific mathematical algorithms that were best fitted to extract changes induced by the presence of cancerous tissue in the backscattered ultrasound waves by training against a mouse model of human ovarian cancer, and retrospective and prospective clinical studies (unpublished data).

Our study was designed to evaluate the classification performance of OVHS. Most of the women studied were referred for presurgical characterisation of ovarian abnormalities. However, patients scheduled for systematic oophorectomy for uterine abnormalities were also included, giving us the opportunity to test OVHS specificity on normal ovaries. OVHS alone performed very well for all FIGO classification stages, with very low numbers of false-negative results leading to 98% sensitivity. That sensitivity was not obtained at the expense of specificity, which remained significantly higher than for TVS alone, even when normal ovaries were not considered. When OVHS was combined with TVS, the number of false-positives obtained with TVS alone for the subgroup composed of benign lesions was lowered significantly. Despite the excellent OVHS sensitivity, its combination with TVS did not significantly change the overall sensitivity for identifying ovarian cancer.

There are several limitations in this study:

First, this study did not assess the real gain provided by an OVHS version that would be embedded in the ultrasound equipment. The physician who performed the TVS did not use OVHS and the gain provided by its use was evaluated theoretically by combining OVHS performance and observers' performance in parallel, considering a diagnosis positive for cancer only when both results were positive and rejecting the cancer when at least one result was negative. This parallel combination led to an underestimation of the overall sensitivity. If used in clinical practice, the TVS + OVHS combination would probably be sequential. The OVHS results would be considered secondarily, as adjuncts to TVS findings. The physicians would probably consider some results positive for cancer that were positive with only one test. For example, for two of our three OVHS false-negative results, TVS had been considered positive for cancer by the physician and vice versa for the eight TVS false-negatives; seven were OVHS-positive.

Second, our sensitivity for TVS alone was higher than that reported in the literature [4]. A possible explanation is that our population was not the general population. Indeed, 71.4% of our patients had ovarian abnormalities and 37.6% were diagnosed with cancer involving the ovaries. This is due to the fact that most of our study centres were referral cancer centres likely to concentrate a high prevalence of cancerous lesion. In addition, all women were scheduled for surgery on the basis of clinical examination, TVS and other criteria eventually including the CA125 blood level

done in days before the TVS for HistoScanning. This represents a bias in the sense that women were not consecutive patients presenting with pelvic symptoms. The rationale backing adoption of this specific design was to avoid interference of the HistoScanning analysis on treatment decision. This is the reason why we did not provide predictive positive or negative values that would be related to the prevalence of cancer in the population studied, which did not reflect the general population. Knowing that, the physicians who performed the TVS had a probable tendency to favour a cancer diagnosis leading to very good TVS sensitivity that could lead to an underestimation of the gain in sensitivity provided by OVHS in combination with TVS compared with TVS alone.

Third, this tendency probably also induced an overestimation of the specificity gain provided by OVHS in combination with TVS, compared with TVS alone. Indeed, our specificity for TVS alone was lower than that reported in the literature [4] and particularly high numbers of endometriosis (7/11, 64%) and teratomas (6/7, 86%) were misclassified, while sensitivities for diagnosing these tumours were reported to be 73% and 84–100%, respectively [35, 36].

We found the performance of OVHS + TVS to be higher than that for CA125 + TVS with regard to sensitivity and comparable with regard to specificity. Pertinently, OVHS is an integral part of the ultrasound examination, while serum assessment for the tumour marker CA125 is an additional test that must be performed at another time with additional costs. Moreover information provided by OVHS is not strictly redundant with CA125 because the combination of TVS + OVHS + CA125 yielded significantly higher specificity than TVS + CA125 (Table 4).

In conclusion, OVHS accuracy was properly validated by comparison with histology, OVHS is highly sensitive in the diagnosis of malignant ovarian masses while maintaining good specificity and it is a promising tool for the non-invasive characterisation of pelvic masses. OVHS is a computer-aided diagnostic system that could be embedded in an ultrasound system to help the physician to discriminate benign from malignant tumours in abnormal ovaries in real time. Its good sensitivity and low false-positive rate, when ovaries were normal, warrants it being tested, in series, with TVS and OVHS under screening conditions.

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