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CLINICAL ARTICLE

Differentiating between benign and malignant adnexal lesions with contrast-enhanced transvaginal ultrasonography

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ABSTRACT

Objective: To analyze the relationship between contrast kinetics in tumorous vessels and lesion histologic type in an attempt to differentiate between malignant and benign disease. *Methods:* In a single-center prospective study, patients who had been referred for elective surgery because of a diagnosis of unilateral and/or bilateral adnexal masses were enrolled at Dr Jan Biziel University Hospital, Bydgoszcz, Poland, between January 2012 and September 2013. Participants underwent contrast-enhanced ultrasonography examination (CEUS). Contrast kinetics were obtained and compared with the neovascularization of the tumor. Accuracy, and positive and negative predictive values were calculated. *Results:* Among 160 enrolled patients, 84 underwent CEUS examination and 51 lesions were studied. Baseline and maximum color Doppler intensities were significantly higher in malignant than in benign tumors ($P < 0.001$ for both). Similarly, the absolute and relative increases in color Doppler intensity were significantly higher in malignant tumors ($P < 0.001$). The estimated positive predictive value was 97.1%, the negative predictive value was 100%, and the accuracy was 100%. Peak enhanced intensity of fractional color Doppler Area and area under the time-intensity curve (S-parameter) correlated significantly with the histology of the lesion ($P < 0.001$). Probability curves demonstrated that higher S-parameter values were correlated with a higher risk of malignancy. *Conclusion:* Transvaginal CEUS is a reliable and reproducible way to differentiate between benign and malignant adnexal lesions.

1. Introduction

Transvaginal ultrasonography remains the preferred method for the evaluation of pelvic masses, and is particularly important in the early diagnosis of adnexal lesions [1]. Its use is advocated by current international guidelines as the first-choice modality in patients with a suspicious isolated ovarian mass [2]. However, for distinguishing benign from malignant tumors, conventional power Doppler ultrasonography has a low sensitivity (50%–80%) and specificity (80%–90%) [3–5] because of inherent limitations, such as the lack of sound reflection from red blood cells and a low signal-to-noise ratio.

Ovarian cancer is associated with poor prognosis, with 5-year survival rates ranging from 27% to 16% for FIGO stage III and IV cancers, respectively, because of delays in diagnosis [6]. Radical surgery and new chemotherapy treatments commonly result in prolongation of survival rather than any significant improvement in the number of patients at an advanced stage who are without disease after 6–8 years [7]. Thus, timely detection and proper diagnosis of early-stage disease is important and has a direct impact on prognosis.

Several observational studies have investigated the role of contrast-enhanced ultrasonography (CEUS) in the diagnosis of ovarian tumors, with results consistently showing a direct correlation between ultrasonography characteristics and tumor angiogenesis, and thus with malignancy progression [8–12]. In light of these findings, the aim of the present study was to analyze the relationship between contrast kinetics in tumorous vessels and lesion histologic type in an attempt to differentiate between malignant and benign disease.

2. Materials and methods

A single-center prospective study was undertaken at Dr Jan Biziel University Hospital, Bydgoszcz, Poland, between January 1, 2012, and September 30, 2013. Consecutively examined women with clinically and ultrasonographically verified adnexal lesions and who had been referred for elective surgery were enrolled. The patients had been hospitalized as a result of a diagnosis of unilateral or bilateral adnexal lesions in the form of ovarian tumors, suspected solid-cystic adnexal

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masses, solid tumors, or similar findings. Patients were eligible for inclusion and imaging with CEUS if, during initial ultrasonography examination, the presence of a unilateral/bilateral solid mass or solid-cystic lesion with a solid component of more than 60% was confirmed. Exclusion criteria were age younger than 18 years, pregnancy, and a general status not enabling elective surgery. The study was approved by the Institutional Review Board and Bioethics Committee of Collegium Medicum, Nicolaus Copernicus University, and written informed consent was acquired from all patients before enrollment.

Size, diameter, echogenicity, and shape were studied for each tumor, and the degree of vascularization of the pathologic lesion was analyzed by means of color Doppler ultrasonography.

Examination commenced with transvaginal and transabdominal real-time gray-scale pelvic ultrasonography, followed by transvaginal color and spectral Doppler ultrasonography. Pelvic masses were systematically examined one after another and were classified according to the International Ovarian Tumor Analysis Group criteria [13]. The maximum diameter was measured and the tumor volume was calculated. All tumors underwent further examination with power Doppler ultrasonography. When a patient had multiple lesions, only the lesion with the greatest vessel count was subjected to CEUS.

CEUS began with administration of the contrast agent (Levovist, Schering AG, Germany) as a bolus of 400 mg/mL over approximately 10 seconds. All patients were examined using the same ultrasonography device (Acuson 128 XP10 with a 7.5-MHz endovaginal probe [Siemens Healthcare, Warsaw, Poland]) and B-mode and color Doppler settings. The examined area covered the entire adnexal mass or, if the entire lesion was too large, the selected cross-section of its solid part. To standardize the analyzed cross-sections, the same three morphologically characteristic components (solid/cystic character of the mass, central/peripheral blood flow, and pulsatility and resistance indices) of every tumor were visualized on gray-scale images. To assure reproducibility and to avoid potential discrepancies with regard to device settings, all CEUS examinations and measurements were performed by one physician (M.S.).

Four-minute video clips were recorded and then analyzed offline. Late-phase microvascular imaging projections were reconstructed with Color Quantifier software (CQ; Kinetic Imaging Ltd, Nottingham, UK) and analyzed to improve lesion detectability. These maximum-intensity projection images depict the overall vascularity of selected regions of interest (ROIs). The ROI was manually selected to cover the entire mass on the harmonic image. The gray-scale intensities of the signals inside the selected ROI were analyzed and the contrast enhancement time-intensity curves for each tumor were constructed, plotted, and analyzed using the CQ software. CQ data were not included in the final analysis when the ROIs could not be selected during CEUS, and when gray-scale ultrasonography could not be standardized in cross-sectional image after contrast agent injection.

The time-intensity curves were normalized by subtracting the mean preinjection (baseline) intensity value from each intensity level (Supplementary Material S1). Four variables were subsequently assessed: 1) the fractional color Doppler area (%CDA), determined for a fixed ROI within each image and defined as the percentage of colored pixels in the given ROI; 2) the time to peak, defined as the time from injection to the peak intensity; 3) the wash-out time, defined as the time between the peak intensity and the point corresponding to the return to baseline; and 4) the area under the curve (AUC) was calculated from arrival of the contrast agent, defined as the point at which an increase in image intensity greater than 10% above the baseline was observed, to the end of the wash-out period. Additionally, the S-parameter was introduced, corresponding to the AUC and being the definite integral in the following form:

$$S = \int_0^{T^*} F_{\%CDA}(t)dt,$$

where T^* is the upper limit of the integration (common to all analyzed plots in some cases). The S-parameter optimally estimates the examination results since the value of S is a joint parameter and is therefore less susceptible to the fluctuations of particular values of the %CDA function. To test if there was linear correlation between the S-parameter and baseline (Y_0) and maximum (Y_{MAX}) %CDA intensities, the Pearson R correlation coefficient was calculated, which was defined as covariance of the variables divided by their standard deviations. Finally, accuracy, positive predictive value, and negative predictive value were also calculated.

Participants were then referred to surgery and treated by means of laparoscopy or laparotomy depending on age, intraoperative histopathology, clinical advancement of the disease, and general status at the surgeon's discretion. Final histologic diagnoses were obtained for all lesions on the basis of the specimens obtained during surgery. Tissues were processed for routine histology. Sections of 5-μm thickness were cut, stained with hematoxylin and eosin, and examined under light microscopy. Tumor types were classified according to the WHO criteria by senior pathologists from pathology department of Dr Jan Biziel University Hospital.

Mean values of the selected variables were calculated. The Mann–Whitney *U* test was used to compare the variance of the acquired contrast kinetics parameters in benign versus malignant lesion analyses. To assess whether the %CDA maximum values were normally distributed, Shapiro-Wilk tests were employed. Consequently, the parametric Cochrane-Cox test for unequal variances was used to compare the mean values of this variable in the studied groups (the hypothesis of variance equality was rejected by the Snedecor F test at $P = 0.003$). In the remaining cases, the non-parametric Mann–Whitney test was used for intergroup comparisons. The results were considered significant at two-sided *P* values of less than 0.05. Statistical analyses were carried out using SPSS 20 (IBM, Armonk, NY).

3. Results

Overall, 160 patients, aged between 18 and 90 years (mean 56.0 ± 14.5) met the enrollment criteria and qualified for surgery for the resection of adnexal lesions. Serous cystadenocarcinomas, mucinous cystadenomas, ovarian metastases, and benign tumors accounted for over 80% of studied tumors according to histopathological specimen analysis (Table 1).

From the initial group, 51 were included in CQ analyses (Fig. 1). The 33 patients with malignant tumors were older (54.5 ± 14.3 years) than were the 18 with benign lesions (45.6 ± 17.2 years), although the difference did not reach statistical significance ($P = 0.06$). The remaining characteristics—body mass index, height, serum creatinine level, diabetes status, and activated partial thromboplastin times—were well balanced between the two groups as confirmed by the Mann–Whitney U-test (data not shown).

Table 1
Pathologic diagnosis of lesions among enrolled women (n = 160).

Lesion	No. (%)
Malignant	139 (86.9)
Serous cystadenocarcinoma	73 (45.6)
Mucinous cystadenocarcinoma	22 (15.8)
Metastatic carcinoma	18 (11.3)
Germ cell carcinoma	10 (6.3)
Clear cell ovarian carcinoma	5 (3.1)
Small cell carcinoma	3 (1.9)
Endometrioid carcinoma	2 (1.2)
Sarcoma	2 (1.2)
Squamous carcinoma	2 (1.2)
Brenner tumor	1 (0.6)
Undifferentiated carcinoma	1 (0.6)
Benign	21 (13.1)
Fibroma	20 (12.5)
Teratoma	1 (0.6)