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● *Original Contribution*

A PILOT STUDY ON DIAGNOSTIC PERFORMANCE OF CONTRAST-ENHANCED ULTRASONOGRAPHY FOR DETECTION OF EARLY CERVICAL CANCER

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Abstract—In this cohort study of 49 women with all stages of cervical cancer and 21 healthy controls, we compared contrast-enhanced ultrasonography (CEUS) filling pattern and semi-quantitative parameters in the two groups. Participants were examined with conventional grayscale and power Doppler ultrasound (US) followed by CEUS, using a 2.5 mL bolus of intravenous contrast agent. CEUS video clips were analyzed with regard to contrast distribution (focal or global) and semi-quantitative parameters. Focal contrast distribution was found in 3% (1/32) of the women with no tumor versus 89% (34/38) of women with histologically detectable tumor. A semi-quantitative analysis showed that the amount of contrast over a period of the whole tumor (area under the curve [AUC[0.92, 95% confidence interval [CI] 0.87–1.0), and the maximal intensity area (AUC 0.94, 95% CI 0.84–1.0) could accurately distinguish tumors from healthy tissue. In conclusion, the CEUS parameters differ significantly between tumors and healthy cervical tissue. (E-mail: kolbrun.palsdottir@ki.se) **© 2018 World Federation for Ultrasound in Medicine & Biology. All rights reserved.**

Key Words: **Cervical carcinoma, Contrast-enhanced ultrasonography, CEUS, Diagnostic accuracy, Filling pattern.**

INTRODUCTION

Imaging is currently in routine use for staging patients with cervical cancer, although it is not considered mandatory by the International Federation for Gynecology and Obstetrics (FIGO) staging criteria (Pecorelli et al. 2009). Magnetic resonance imaging (MRI) is the most commonly used diagnostic modality for examining these patients, although ultrasound (US) has proven to be at least as accurate in evaluating local tumor extension (Epstein et al. 2013). US might be superior to MRI in detecting small tumors (<1 cm), such as are suitable for fertility-sparing surgery (tumor <2 cm, distance from cranial tumor margin to internal cervical os >1 cm) (Epstein et al. 2013; Fischerova et al. 2008). Nevertheless, there is need to improve the diagnostic certainty in the detection and assessment of small tumors in women opting for fertility-sparing surgery.

Contrast-enhanced ultrasonography (CEUS) has been developed to use as a complement to the standard B-mode US examination and gives an extended real-time vision into the circulation of the organ of interest. The examination with contrast agent makes it possible to visualize much smaller vessels than can be detected by color or power Doppler (Gorce et al. 2000). The dynamic character makes it possible to estimate circulatory changes both subjectively and quantitatively during a certain time lapse. There are a number of suggested clinical applications of the method, including detection of perfusion abnormalities related to tumors, fibrosis and ischemia in the heart and kidneys (Bertolotto et al. 2015; Sidhu et al. 2018). The most widely accepted use is for differential diagnosis of focal liver lesions (Jang et al. 2009; Takahashi et al. 2013). These lesions can now be specified and classified as benign or malignant by CEUS: Most malignant lesions appear hypoenhanced in the venous phase of CEUS, but the majority of benign focal lesions are iso- or hyperenhanced (Corvino et al. 2015; Leen et al. 2006; Strobel et al. 2008). According to the updated version of European Federation of Societies for Ultrasound in Medicine and Biology guidelines from 2017 there are no recommended clinical indications for the use of CEUS in gynecology (Sidhu et al. 2018). Malignant tumors in the uterine cervix are well vascularized in contrast to normal cervical stroma (Testa et al. 2004). It has not yet been established whether any diagnostic advantage may be gained by adding CEUS to

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conventional imaging (grayscale and color or power Doppler) in patients with cervical cancer. A limited number of studies have been published on the use of CEUS in patients with cervical cancer. In a small sample (n = 10), cervical cancer was better defined subjectively with CEUS in 40% of cases compared with conventional imaging (Testa et al. 2005). In another study a significant correlation was found between CEUS peak intensity and microvessel density (MVD) as a measure of tumor angiogenesis (Zheng et al. 2016). A third study evaluated the use of CEUS in monitoring the response to antiangiogenic therapy in cervical tumors (Lamuraglia et al. 2010). However, we have not found any studies describing the contrast distribution and quantitative CEUS parameters in healthy cervical tissue compared with cervical tumors.

OBJECTIVES

The primary aim of our study was to describe the qualitative (contrast distribution; *i.e.*, "filling pattern") and semiquantitative parameters acquired from the time intensity curve (TIC) in healthy cervical tissue and in cervical cancer. Our secondary aim was to assess the diagnostic accuracy of CEUS compared with conventional US for cervical cancer tumor detection and to evaluate interobserver agreement on the interpretation of the CEUS filling pattern.

METHODS

Our prospective cohort study included women with all clinical stages of cervical cancer referred to Karolinska University Hospital for treatment. All the women had a diagnosis of invasive cervical cancer based on a cervical biopsy or cervical cone-biopsy (please see the routine algorithm for the investigation of cervical cancer at our institution in Fig. 1). Clinical information was collected regarding tumor stage, treatment and histology in cases where surgery was performed. Healthy controls were recruited through an advertisement circulated among hospital personnel. The study began in July 2012, and the last participants were recruited in July 2015. Ethics approval (EPN-2011/1925) was obtained before undertaking the study, and informed written consent was given by all participants. All patients were clinically staged according to the FIGO diagnostic criteria for cervical cancer (Pecorelli et al. 2009). Participants were examined with ultrasonography by E.E., who has over 20 y of experience in this field, and K.P., who has 4 y of experience as a second-opinion ultrasonographist. Cervical cancer US examination methodology has previously been described (Fischerova 2011). All examinations were performed transvaginally or transrectally, with each woman lying in a lithotomy position after having emptying her bladder, according to a predefined study protocol.

Conventional grayscale and power Doppler US examination

A conventional grayscale and power Doppler examination was performed using a GE Voluson E8 (GE Medical Systems, Zipf, Austria) with a 5–9 MHz, 3D transvaginal probe (RIC 5-9-D). Video clips, 3D volumes and still images of tumors using both grayscale and power Doppler US were systematically collected for each woman. The power Doppler pulse repetition frequency (PRF) was set to 0.6, but adjusted to 0.9 in cases of over blooming or at 0.3 where there were penetration problems to optimize the visualization of vascularity in the tumor. The tumors were scanned in both the transversal and longitudinal planes. The following data were recorded immediately after the examination in a case report form: Tumor presence (yes/no), size (three perpendicular diameters: anteroposterior, cervicofundal and lateral) and vascularization using power Doppler (color score 1 = no flow, color score 2 = sparse flow, color score 3 = moderate flow, color score 4 = abundant flow).

CEUS examination

The CEUS examination was performed using an iU22 US system (Philips Healthcare, Best, The Netherlands) with a 3–9 MHz, 2D transducer. We used a SonoVue contrast agent (Bracco, Milan, Italy), the most commonly used US

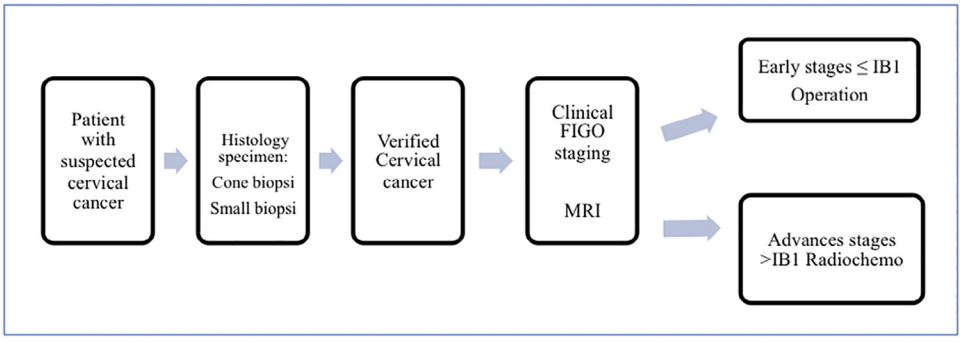

Fig. 1. Flowchart showing the routine algorithm for the investigation of cervical cancer at our institution.

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