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Can quantitative contrast-enhanced ultrasonography predict cervical tumor response to neoadjuvant chemotherapy?

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ABSTRACT

Objective: To evaluate the feasibility of quantitative contrast-enhanced ultrasonography (CEUS) for predicting and assessing cervical tumor response to neoadjuvant chemotherapy (NACT).
Methods: Thirty-eight cases with stage IB2 or IIA cervical cancer were studied using CEUS before and after one cycle of NACT. The quantitative CEUS parameters maximum intensity (IMAX), rise time (RT), time to peak (TTP), and mean transit time (MTT) were compared between cervical tumors and myometrium (reference zone) using Sonoliver software. Absolute and relative changes in quantitative CEUS parameters were also compared among complete response, partial response, and non-responsive groups. Correlations between pre-treatment IMAX and changes in quantitative parameters were assessed after one cycle of NACT.
Results: There were significant changes in cervical tumor IMAX ($P < 0.001$), RT ($P < 0.05$), and TTP ($P < 0.05$) after one cycle of NACT. According to the Response Evaluation Criteria In Solid Tumors guidelines, the enrollments were divided into complete response, partial response, stable disease and progressive disease groups. There were no significant differences in quantitative CEUS parameters among complete response, partial response, and non-responsive groups ($P > 0.05$). In the stable disease group (n = 17), cervical tumor IMAX, RT, and TTP decreased significantly after NACT ($P < 0.001$). The absolute and percentage changes in IMAX were positively correlated with pre-treatment IMAX in all 38 patients ($r = 0.576$, $P < 0.001$ and $r = 0.429$, $P < 0.001$).
Conclusion: Quantitative CEUS analysis can reveal changes in tumor perfusion following NACT. Tumor perfusion values changes likely precede size changes during the NACT course, and pre-treatment IMAX may be a valuable predictor of cervical tumor perfusion response to NACT with a great decrease in IMAX correlated with better perfusion response.

1. Introduction

Cervical cancer is the fourth most common female cancer, with about 527,600 new cases and 265,700 deaths reported worldwide in 2012 [1]. The benefits and risks of neoadjuvant chemotherapy (NACT) for the treatment of locally advanced cervical cancer remain uncertain. NACT followed by radical surgery has been studied as a means to reduce tumor bulk and prolong survival in patients with International Federation of Gynecology and Obstetrics (FIGO) stage IB2-IIB cervical cancer [2,3]. NACT followed by radical hysterectomy is considered an optional treatment modality for stage IB2 or IIA cervical cancer in our Department of Gynecological Oncology. Objective factors associated with the response to NACT may prove valuable for selecting the optimal treatment [4].

Clinical criteria for monitoring the response of tumors to treatment is based on change in size according to the Response Evaluation Criteria In Solid Tumors (RECIST) guidelines [5,6]. However, anatomic assessment has been found to be unsatisfactory, and it is difficult to differentiate necrotic tumor tissue and fibrotic scar from residual viable tumor tissue using morphologic imaging techniques such as positron emission tomography (PET), magnetic resonance imaging (MRI), computed tomography (CT), and conventional ultrasound [5,7]. In addition, functional changes likely precede size changes as some anticancer treatments have effects on the tumor vasculature in addition to malignant clonogenic cells [8]. Recently, a number of functional imaging techniques have been

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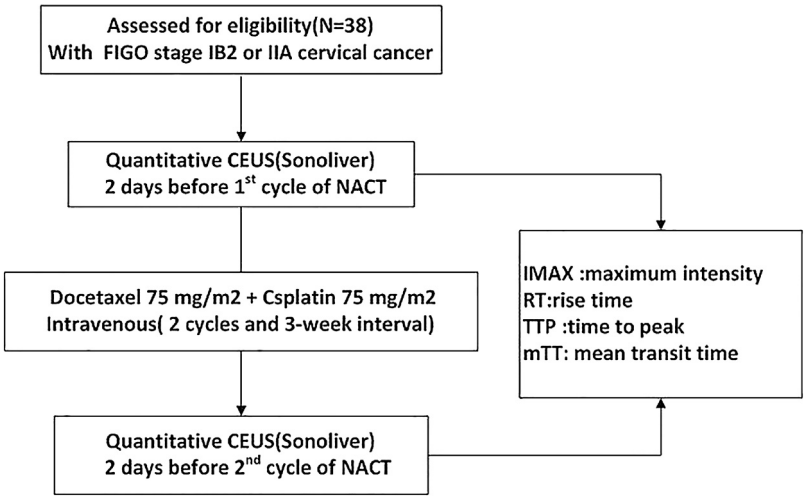

Fig. 1. Flow diagram of study enrollment.

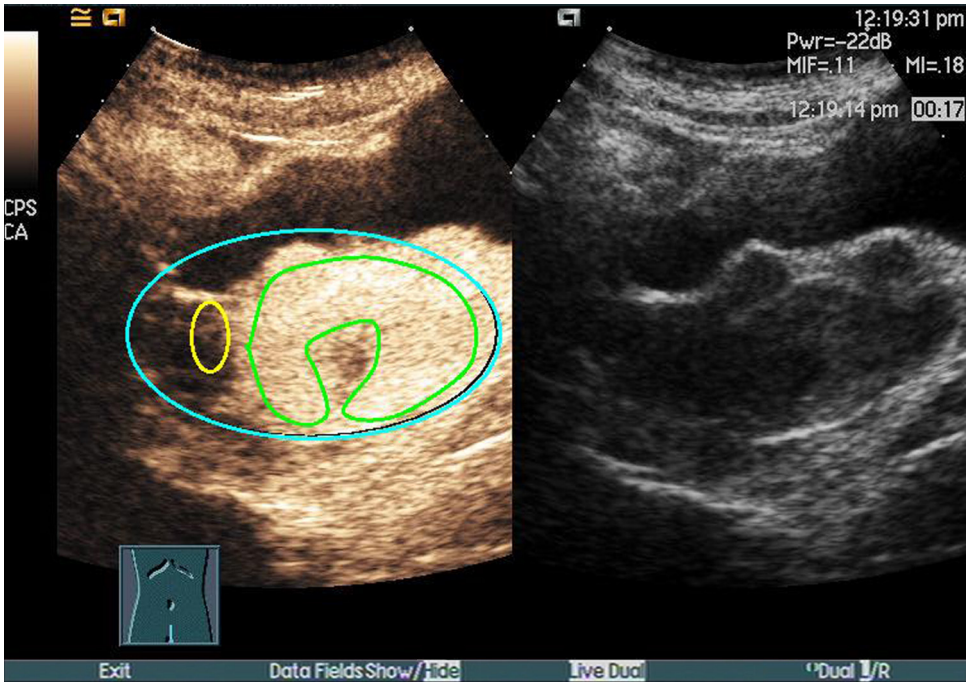

Fig. 2. Representative Sonoliver (left) and the native (right) contrast-enhanced ultrasonography images of a cervical tumor in the early phase after contrast agent injection (17 s). Three regions of interest (ROIs) were drawn: a blue ROI delimiting the region where motion compensation is applied, a green ROI encompassing almost the entire tumor from the best identified frame during enhancement (avoiding large vessels and necrotic regions), and a yellow ROI showing the myometrium (reference region) at near the same depth as the cervical tumor.

used to evaluate tumor perfusion, including contrast-enhanced CT, dynamic contrast-enhanced (DCE) MRI, and contrast-enhanced ultrasonography (CEUS) [9–11]. However, high concentrations of CT contrast agents together with relatively high doses of ionizing radiation limit the application of CT, while consistent DCE MRI methodologies have not been developed to ensure reproducibility for response evaluation [11]. Alternatively, CEUS using SonoVue agents (Bracco, Milan, Italy) has been suggested as an attractive technique to provide both morphological and functional information on tumor response without the risks conferred by ionizing radiation, particularly for repeated imaging.

The recent development of analytic software for CEUS has further improved response evaluation by providing quantitative parameters of contrast agent kinetics within the tumor vasculature. Indeed, the value of quantitative CEUS analysis for evaluation of tumor angiogenesis and response to anti-angiogenic agents has been demonstrated in both animal and clinical studies [12–14]. In the present study, quantitative CEUS analysis was used to investigate the changes in perfusion of cervical tumors after one cycle of NACT and to identify parameters for early prediction and response assessment following NACT.

2. Materials and methods

2.1. Patients

Between April 2011 and July 2013, 38 eligible patients (median age [interquartile range]; 46 years [42–55]) with histologically confirmed cervical cancer were prospectively enrolled. All patients underwent cervical biopsy on either indication of clinically sus-