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Ultrasonic histogram assessment of early response to concurrent chemo-radiotherapy in patients with locally advanced cervical cancer: a feasibility study

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ABSTRACT

Purpose: To monitor early response for locally advanced cervical cancers undergoing concurrent chemo-radiotherapy (CCRT) by ultrasonic histogram.

Methods: B-mode ultrasound examinations were performed at 4 time points in thirty-four patients during CCRT. Six ultrasonic histogram parameters were used to assess the echogenicity, homogeneity and heterogeneity of tumors.

Results: I_{peak} increased rapidly since the first week after therapy initiation, whereas W_{low}, W_{high} and A_{high} changed significantly at the second week. The average ultrasonic histogram progressively moved toward the right and converted into more symmetrical shape.

Conclusion: Ultrasonic histogram could be served as a potential marker to monitor early response during CCRT.

1. Introduction

Concurrent chemo-radiotherapy (CCRT)has been considered as the standard therapy for advanced cervical cancer since 1999 [1]. Response to CCRT is still largely determined by tracking changes in tumor size with conventional imaging techniques, such as ultrasound, computed tomography and magnetic resonance imaging (MRI). However, these morphological changes in gross tumor size or volume significantly lag behind biological and molecular changes that occur early in treatment responders [2, 3]. Nowadays, recent advances in functional imaging (diffusion-weighted MRI, dynamic contrast-enhanced MRI, 18F-fluorodeoxyglucose positron emission tomography) enable us to provide the information of microstructure and microcirculation alterations during the anti-cancer treatments, and have thus opened up a new avenue to monitor and predict early response [4–6]. Nevertheless, the high cost, the technical complexity, increased radiation burden or potential contrast agent's adverse reaction limited their routine surveillance. Therefore, ultrasound still remains the first choice for the evaluation of therapeutic efficacy, especially in the developing countries.

It is well-established that sonographic features of malignant tumors are different from those of normal tissues or benign lesions in the B-mode image. Cervical tumor can be diagnosed on the basis of echogenicity and heterogeneity relative to surrounding normal cervical tissue. With the effective non-surgical anti-cancer therapy, series of pathophysiological processes may develop by means of inflammation, necrosis and apoptosis, and the sonographic features within the tumor will change as well. In conventional ultrasound, the echogenicity and heterogeneity of tumor were usually interpreted by subjective evaluation [7–9], nevertheless, these subtle changes may be difficult to capture through visual inspection in the early period of treatment. Ultrasonic histogram is known as a graphic distribution, which shows the number of pixels in the B-mode image among different grayscale values, based on the quantitative measurement of the probability of each gray level. As some pathologic processes may affect the echo-intensity, ultrasonic histogram has shown good results in the identification of abnormalities such as hepatopathy, thyroiditis and breast lesions [10–12]. However, previous histograms mostly provided the single variable of mean gray value, failing to afford accurate evaluation of heterogeneity.

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In a study of apparent diffusion coefficient histogram shape analysis, Meng et al. demonstrated that tumor response was associated with the decrease of tumor cell morphological heterogeneity in cervical cancer after effective therapy [13].Recently, Yang et al. developed a family of six sonographic parameters derived from echo histograms, reflecting echo-intensity distributions, echogenicity, homogeneity and heterogeneity, in which both echogenicity and heterogeneity of normal parotid glands went up after radiation [14]. Furthermore, these parameters exhibited excellent diagnostic accuracy to distinguish acute toxicity from late toxicity in radiation-induced parotid-gland [15]. Therefore, with the superiority of quantitative measurement of echogenicity and heterogeneity, we hypothesized that ultrasonic histogram could be utilized to monitor tumor response during CCRT.

Up to date, there was no report investigating change of ultrasonic histogram for monitoring cervical cancer response to CCRT. The purpose of this study was to prospectively investigate the changes in echo-intensity histogram parameters with cervical cancer patients undergoing CCRT, and to evaluate the potential role of ultrasonic histogram as an early imaging biomarker for therapy response.

2. Materials and methods

2.1. Study population

Between October 2014 and January 2017, 34 patients with histologically confirmed cervical cancer scheduled to receive CCRT in our hospital were enrolled. Each patient was staged according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO). The inclusion criteria were as follows: (1) age over 21, (2) FIGO Stage IB to IV, (3) no history of prior chemotherapy or radiotherapy.

This study was approved by our institutional review board and in accordance with the ethical standards of the World Medical Association (Declaration of Helsinki). Written informed consents were obtained from all patients.

2.2. Concurrent chemo-radiotherapy

Thirty-four patients were treated with a combination of radiotherapy and chemotherapy. Radiotherapy consisted of external beam radiotherapy and intracavitary brachytherapy. External beam radiotherapy was delivered to the whole pelvis with a total dose of 50 Gy (2 Gy per fraction, 5 fractions per week) and accompanied by concurrent chemotherapy as follows: three-four cycles of every 2 weeks Nedaplatin (40–60 mg/m^2) plus Paclitaxel (80 mg/m^2). Intracavitary brachytherapy was initiated after an EBRT dose of 50 Gy and delivered twice a week with a dose of 5 Gy at point A (6 fractions, total dose 30 Gy). The definition of point A follows the American Brachytherapy Society recommendation [16]. The entire CCRT treatment for each patient was completed within 8 weeks.

2.3. Treatment response evaluation

The treatment response depended on the follow-up with pelvic examinations (vaginal and rectal examination), serum marker evaluations (such as squamous cell carcinoma antigen (SCC-Ag) and carcinoembryonic antigen (CEA)) and pelvic MRI outcomes prior to and immediately after therapy completion. All MRIs were performed with a Philips Achieva 3.0-T MRI scanner (Philips Healthcare, Best, The Netherlands) with a 16-channel torso phased-array body coil. The change of tumor size was calculated according to the following equation: change in tumor size % = (pre-longest diameter − post-longest diameter) / pre-longest diameter × 100%. The clinical responses were classified using the Response Evaluation Criteria in Solid Tumors 1.1 criteria [17] in the following 4 categories: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). CR is defined as no residual cancer, PR as at least a 30% decrease in the sum of diameters of the cancer, PD as at least 20% increase and SD as no sufficient shrinkage to qualify for PR or sufficient increase to qualify for PD.

2.4. Ultrasound imaging protocol

Ultrasound examinations were acquired using GE Voluson E8 ultrasound machine (GE Medical Systems, Milwaukee, WI, USA) with a 3D/4D endocavitary convex array transducer (GE RIC5-9, bandwidth 5–9 MHz). All ultrasound data were acquired with the same settings: 5.0 cm depth,1 focal zone, 7 Gy map, −15 gain, 121° angle, 3 persist, 2 enhance, 20 reject and 7 dynamic control. Each patient received B-mode transvaginal ultrasound examinations at 4 time points (prior to CCRT, at 1 week and 2 weeks during CCRT, as well as within 1-week post CCRT). Cervical tumoral tissue was identified as a mass with heterogeneous echogenicity and irregular borders with disruption of the cervical canal. The gray-scale image of the sagittal view along the longest diameter of the cancer was obtained. All images were saved in 8-bit gray scale and the intensity ranged between 0 and 255. Each B-mode image contained 976 × 735 pixels; and the size of each pixel was both 0.106 mm in the lateral and depth (beam) direction.

2.5. Echo-intensity histogram analysis of the ultrasound image

All B-mode images of the whole cervical tumors were manually contoured by radiologists (Y.X. and L.Z.) as the region-of-interest (ROI), whereas a fixed ROI of 0.5 cm (width) × 0.5 cm (depth) was used for the surrounding normal cervical tissue, and the histograms were subsequently generated. The ultrasonic histograms and parameters were analyzed by in-house signal processing software written in MatLab (Mathworks, Natick, Massachusetts, USA).

Based on the ultrasonic histogram model introduced by Yang et al. studies [14, 15], six histogram parameters were used to provide quantitative assessment of the echogenicity and heterogeneity of the cervical cancer (Fig. 1). The I_{peak} means the peak intensity value of the histogram. W_{-3dB} is the -3 dB intensity width of the histogram. W_{low} and W_{high} represent the width of the low-intensity (< 50% I_{peak}) and the high-intensity (> 50% I_{peak}) portions of the histogram, respectively. A_{low} and A_{high} characterize the area under the low-intensity and high-intensity portions of the curve. These parameters characterize the echogenicity (I_{peak}), homogeneity (W_{-3dB}), and heterogeneity (W_{low}, W_{high}, A_{low}, and A_{high}) of cervical cancer. All histograms are normalized to the peak intensity I_{peak}.

2.6. Reproducibility study

We chose ten ultrasound images from 10 cervical cancers for reproducibility study. Radiologists (Y.X. and L.Z.) were asked to manually contour the region of whole cervical tumors independently for each image. The parameters derived from the corresponding ultrasonic histogram were computed to evaluate the inter-observer variability. Furthermore, radiologist (Y.X.) was asked to manually contour the ROI of the same image twice at different times. The ultrasonic histogram parameters were calculated to assess the intra-observer variability.

2.7. Statistical analysis

Statistical analysis was performed using SPSS software version 22.0 (SPSS Inc., Chicago, IL, USA). Student's *t*-test was used to compare differences in the histogram parameters between cervical cancers and normal cervical tissues. Repeated measures analysis of variance and student's *t*-test were used to the multiple comparisons in the histograms parameters at each time point. A two-sided $p < .05$ was considered to be statistically significant. The intra-class correlation coefficient (ICC) with a 95% confidence internal (95% CI) was adopted to assess inter-observer and intra-observer variability of measurements.