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Original article

A prospective study of DWI, DCE-MRI and FDG PET imaging for target delineation in brachytherapy for cervical cancer

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ABSTRACT

Background and purpose: We examined the utility of dynamic contrast-enhanced MRI (DCE-MRI), diffusion-weighted MRI (DWI), and FDG-PET imaging for brachytherapy target delineation in patients with locally advanced cervical cancer.

Materials and methods: Twenty-two patients had DWI, DCE-MRI, and FDG-PET/CT scans after brachytherapy applicator insertion, in addition to standard T2-weighted (T2w) 3T MRI. Gross tumor volume (GTV_B) and high-risk clinical target volume (HRCTV) were contoured first on T2w images, and then modified if indicated upon review of DWI/DCE-MRI/FDG-PET images by two observers. The primary endpoint was utility, determined by the number of patients whose volumes were modified, and interobserver variability.

Results: Eleven patients' T2w-GTV_B were modified based on DWI/DCE-MRI/FDG-PET by observer 1, due to clearer demarcation (7) and residual disease not well visualized on T2w MRI (4). GTV_B was modified in 17 patients by observer 2 (11 and 6, respectively). Incorporation of functional imaging improved the conformity index (CI) for GTV_B from 0.54 (T2w alone) to 0.65 ($P = 0.003$). HRCTV was modified in 3 and 8 patients by observers 1 and 2, respectively, with a trend toward higher CI using functional imaging (0.71 to 0.76, $P = 0.06$).

Conclusions: DWI/DCE-MRI/FDG-PET imaging as a supplement to T2w MRI decreased interobserver variability in GTV_B delineation.

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The standard treatment of locally advanced cervical cancer consists of external beam radiotherapy (EBRT), concurrent chemotherapy, and brachytherapy. Image-guided adaptive brachytherapy has yielded higher local control and survival rates compared to historical control [1–4]. Many centers have adopted the GEC-ESTRO recommendations for brachytherapy target delineation, where T2-weighted (T2w) MRI remains the gold standard for tumor visualization [5,6]. Despite this, recent studies using T2w MRI reported significant uncertainties in brachytherapy target delineation, and poor interobserver variability with mean conformity indices (CI) of only 0.58–0.60 for gross tumor volume at brachytherapy (GTV_B), and 0.39–0.79 (mostly between 0.70–0.79) for high-risk clinical target volume (HRCTV) [7–11].

Functional imaging by diffusion-weighted MRI (DWI) and dynamic contrast-enhanced MRI (DCE-MRI) in combination with conventional T2w MRI can improve cervical tumor distinction [12–15]. DWI displays information about water mobility in tissue, tissue cellularity, and integrity of cellular membranes [12]. Tumors usually exhibit restricted diffusion. DCE-MRI measures temporal changes in MR signal intensity associated with intravenous injection of an extracellularly confined contrast agent, reflecting variations in tissue perfusion, extracellular space fraction, microvascular permeability, and angiogenesis [16]. Small cervical tumors usually enhance homogeneously and earlier than the normal cervical stroma, whereas large tumors are often non-enhancing (necrotic) and surrounded by an enhancing rim [12].

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^{18}Fluorodeoxyglucose positron emission tomography (FDG-PET) imaging detects disease based on metabolic function [17]. While T2w MRI has higher sensitivity than PET-CT (86% versus 63%) in predicting residual disease in the cervix at the time of surgery in patients with locally advanced cervical cancer treated with neoadjuvant treatment (majority with EBRT and chemotherapy), FDG-PET/CT has higher specificity (81% versus 36%) [18].

The role of these functional imaging modalities in MRI-guided brachytherapy of cervical cancer as a supplement to T2w MRI, especially in the learning period, has not been widely investigated. We hypothesized that DCE-MRI, DWI and FDG-PET imaging in combination with T2w MRI would reduce uncertainties in brachytherapy target delineation. The aim of this study was to determine the utility of DCE-MRI, DWI and FDG-PET imaging (as a supplement to T2w MRI) for brachytherapy target delineation in patients with locally advanced cervical cancer.

Materials and methods

This prospective study was approved by the institutional ethics review board.

Twenty-two patients with FIGO stage IB2-IVA cervical squamous cell carcinoma or adenocarcinoma planned for definitive chemoradiation were enrolled in a prospective study between October 2012-July 2015. All patients were treated with standard EBRT (45–50.4 Gy in 1.8–2 Gy daily fractions) to the pelvis ± paraaortic lymph nodes, weekly cisplatin chemotherapy (40 mg/m^2) during EBRT, and intracavitary/interstitial brachytherapy (initiated usually within 1 week of completing EBRT). A custom-made MR-compatible intrauterine applicator, ring and tandem applicator ± interstitial needles (Elekta AB, Stockholm, Sweden), or the Syed-Neblett template with vaginal obturator and interstitial needles (Best Medical Systems, Inc., Springfield, USA) were used for brachytherapy. Prior to 2014, brachytherapy was delivered using a pulsed dose rate technique to 35–40 Gy. Following this, a high dose rate (HDR) technique was used to deliver 28 Gy in 4 fractions, with 2 fractions per insertion, and adaptive replanning prior to each fraction.

Imaging protocol

The following study images were acquired: DWI, DCE-MRI, and FDG-PET/CT scan on the day of brachytherapy after applicator insertion in addition to standard T2w MRI; FDG-PET/CT scan 3 months post completion of treatment; and multiparametric MRI (T2w, DCE-MRI and DWI) every 3 months for 2 years following completion of treatment. Follow-up study MRIs were performed every 3 months to enable correlation of the site of recurrent/residual disease with study imaging findings at the time of brachytherapy.

Patients were imaged supine with a torso phased-array coil placed anterior, and spine matrix array coil placed posterior, using a 3 Tesla Verio (Siemens Medical Systems, Erlangen, DE) with VQ gradients (40 mT/m peak amplitude; 200 T/m/s peak slew rate). Pulse sequences were acquired as follows:

(A) axial 2D T2w turbo-spin echo (repetition time msec/echo time msec, 4500/102, 320 × 320 matrix, 20 cm field of view (FOV), 0.6 mm in-plane resolution, 50 slices, 5 min 44 s);
(B) coronal 2D T2w turbo-spin echo (TR/TE = 4000/98 ms, 256 × 256 matrix, 20 cm FOV, 0.8 mm in-plane resolution, 35 slices, 3 min 50 s);
(C) 3D sagittal SPACE (Sampling Perfection with Application optimized Contrast using different flip angle Evolutions, TR/TE = 1200/133 ms, 320 × 323 × 120 matrix, 25.6 × 25.6 × 9.6 cm FOV, 0.8 mm isotropic resolution, 5 min 35 s).
(D) axial 2D diffusion-weighted single-shot echo-planar imaging (TR/TE = 4400/83 ms, 128 × 128 matrix, 20 cm FOV, 1.6 mm in-plane resolution, 14 slices, 4 *b*-values of 0, 100, 600, 1000 s/mm^2 with isotropic sampling in 3 directions, water-selective excitation, 4 min 39 s).
(E) variable flip-angle T1 mapping (3D-FLASH termed Fast Low Angle Shot; TR/TE = 25/1.71 ms, 128 × 128 × 20 matrix, 20 × 20 × 6 cm FOV, 1.6 mm in-plane resolution, flip angles of 2, 10, 20, 30 degrees, 48 s per flip angle)
(F) DCE-MRI (3D-FLASH, TR/TE = 4.3/1.71 ms, 128 × 128 × 20 matrix, 20 × 20 × 6 cm FOV, 1.6 mm in-plane resolution, 20° flip angle, 50 repetitions, 4.8 s per repetition, 4 min 2 s). Gadopentetate dimeglumine (Gd-DTPA) was infused at a rate of 4 mL/s.

Quantitative acquisitions shared matching geometric features. The slice thickness was 3 mm for all acquisitions, except SPACE. A parallel imaging factor of 2 was used for all acquisitions.

FDG was then administered intravenously at a dose of 5 MBq/kg, 60 min prior to imaging using an integrated PET/CT system (Discovery 610; GE Healthcare). CT was performed first, with a 2.5 mm slice thickness. A PET emission scan was then acquired for 4 min per bed position, at 2–3 bed positions per patient on the day of brachytherapy; and for 3 min per bed position at 6–8 bed positions at 3-month follow-up. PET image datasets were reconstructed using CT data for attenuation correction.

Image analysis

Apparent diffusion coefficient (ADC) maps were generated from the diffusion-weighted images using in-line processing and *b* values of 0, 100, 600 and 1000 s/mm^2 (Siemens Medical Systems). For DCE-MRI, 3D-FLASH magnitude signal time-courses were converted to Gd-DTPA concentration profiles on a per voxel basis, incorporating T_1 mapping [19,20]. The modified Tofts model [21] was fitted to the concentration profiles to generate maps of K^{trans} (the transfer constant from the blood plasma into the extracellular extravascular space), incorporating individualized estimates of input functions using the 3D-FLASH phase signal from the external iliac arteries [22].

Target delineation

GTV_B and HRCTV were contoured initially as per GEC-ESTRO guidelines [5] by a single observer (observer 1) on the day of brachytherapy, using only the axial T2w MR images without viewing the functional study images. The DWI, DWI-derived ADC map, DCE-MRI and FDG-PET/CT images were then reviewed and registered to the T2w MR images based on the applicator; GTV_B and/or HRCTV were modified in real-time to define the target more accurately, and/or include areas of suspected disease on DWI/DCE-MRI/FDG-PET not obvious on T2w MR. Observers were instructed to use the ADC map to identify areas of restricted diffusion as tumor. DCE-MRI signal images were used to identify either small tumors that enhanced homogeneous and earlier than the normal cervical stroma, or larger (often non-enhancing/necrotic) tumors surrounded by an enhancing rim [12]. In the latter case, the entire volume encompassed by the enhancing rim was contoured as GTV_B. Patients were treated with an optimized brachytherapy plan based on contours that incorporated the functional study imaging findings. To assess interobserver variability, target delineation was performed in the same and blinded manner by another observer (observer 2) after brachytherapy treatment.

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