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Early clinical outcomes of ultrasound-guided CT-planned high-dose-rate interstitial brachytherapy for primary locally advanced cervical cancer

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ABSTRACT

PURPOSE: To report early clinical outcomes of high-dose-rate interstitial image-guided brachytherapy (BT) in the definitive management of locally advanced cervical cancer.

METHODS: We retrospectively analyzed 31 locally advanced cervical cancer patients treated at our institution between January 2010 and April 2013. About 88% had advanced disease based on the International Federation of Gynecology and Obstetrics guidelines, and 87% received concurrent chemotherapy. All patients were treated with external beam radiation therapy to a median dose of 45 Gy (range, 39.6–58 Gy) before receiving BT. High-dose-rate BT was delivered in a single implant to a median dose of 6 Gy × five fractions to a CT-defined volume. Median total equivalent 2-Gy dose, dose covered by 90% of the high-risk clinical target volume (HR-CTV D_{90}), and HR-CTV were 84, 87.4, and 49.9 cc, respectively. Kaplan–Meier method was used for actuarial survival analysis, and toxicity was graded using Common Terminology Criteria for Adverse Events, version 4.0.

RESULTS: Median followup was 19.3 months. Two-year actuarial local control, regional control, and distant metastasis (DM) were 90%, 93%, and 23.6%, respectively. Two-year disease-free survival was 55%. Genitourinary, gastrointestinal, or gynecologic Grade 3 toxicity was seen in 5 patients (3 T4a and 2 T3b) for crude rates of 13%, 7%, and 3%, respectively. Stratifying HR-CTV by <30 and >30 cc and then by HR-CTV D_{90} of <85, 85–90, and >90 Gy showed that 100% of the local failures, regional failures, DM, and G3 toxicity occurred in >30 cc group. The rate of DM was also significantly higher in the >30 cc group ($p = 0.036$).

CONCLUSIONS: An interstitial approach can achieve excellent outcomes in cases where intracavitary and/or hybrid approaches are either not suitable or not available.

Keywords: Cervical cancer; High-dose-rate; Interstitial; Image-guided brachytherapy

Introduction

Radiation therapy (RT) is a mainstay in the definitive treatment of locally advanced cervical cancer. It consists of a combined course of external beam radiation therapy (EBRT) with concurrent chemotherapy and a brachytherapy (BT) boost. The BT component of treatment can be performed using an intracavitary (IC), interstitial (IS), or hybrid (IC and IS) implant. IC/hybrid approaches are most commonly used, whereas IS BT is the most versatile of all the techniques. It is generally considered in situations where the extent of residual disease at the time of BT cannot be adequately encompassed with an IC or hybrid approach, and/or the patient's anatomy cannot accommodate a standard IC applicator (1, 2).

Traditionally, BT was performed using two-dimensional imaging and prescribing dose to Point A. In 2005, the Groupe Euopéen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) published guidelines introducing and defining concepts for three-dimensional (3D) volume-based approaches for cervical cancer BT (3, 4). Prospective single-institution results using volume-based prescriptions to a high-risk clinical

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target volume (HR-CTV) and 3D evaluation of dose distribution in organs at risk dose have demonstrated significant improvements in local control (LC) and reductions in late-term gastrointestinal and genitourinary (GU) toxicities (5–13). These image-guided brachytherapy (IGBT) studies have predominantly used either IC and/or hybrid applicators. There are limited data using 3D-based IS BT. In this study, we report clinical outcomes of cervical cancer patients treated with image-guided high-dose-rate (HDR) IS BT as part of the definitive management of their disease.

Methods

An institutional review board approved–retrospective study was conducted on 31 consecutive patients treated in the Department of Radiation Oncology at the University of California, Los Angeles, between January 2010 and April 2013. All patients had histologically proven cervical cancer and underwent imaging and clinical examination for staging purposes at the initial consultation. For staging, 24 patients underwent positron emission tomography/CT, 4 CT chest/abdomen/pelvis, 3 CT abdomen/pelvis and a chest X-ray, and 1 chest X-ray/cystoscopy/proctosigmoidoscopy/pelvic lymphadenectomy. Cystoscopy and proctosigmoidoscopy were performed in some patients but not routinely performed on all patients. If insurance authorization would allow, imaging of the pelvis was performed before BT, with 11 of 31 (35%) patients undergoing MRI.

Radiation treatment

Patients were first treated with EBRT to a median dose of 45 Gy (range, 36–58 Gy). Of the 31 patients, 10 were treated with intensity-modulated RT, 18 with 3D-conformal four-field box technique using high-energy beams, and 3 with 3D-conformal four-field box technique using high-energy beams with a midline block. Most patients were treated with concurrent chemotherapy during their EBRT (87%). This was then followed by an IS implant. Indications for performing an IS implant were most commonly because of residual disease that could not be encompassed using an IC approach (22 of 31), anatomy that could not accommodate an IC applicator (6 of 31), cases where an outside radiation oncologist could not successfully perform an IC implant (1 of 31), and when logistical considerations of being able to complete all the BT in one inpatient stay were necessary (2 of 31). As our clinic does not have a hybrid applicator, this was not a treatment option available for our patients.

For the BT implant, patients had an epidural and sedation, and the epidural was kept in place for postprocedure pain control. Transrectal ultrasound was used to guide placement of the flexiguides (Best Medical International 15G, Springfield, VA) through a Syedd–Neblett template in real time along with intermittent anterior and lateral fluoroscopy to confirm appropriate catheter positioning (Fig. 1). The mean number of flexiguides per patient was 27.5 (median, 26; range, 15–41). After the implant procedure, contouring was performed on CT simulation images. MRI was used to assist with defining an HR-CTV when available as per GEC-ESTRO guidelines; however, all contours were drawn on the CT (Fig. 1) (14). A CTVopti was defined as the HR-CTV plus a variable volume of uterus extending along the tandem superior to the highest extent of the HR-CTV (typically about 2–3 cm). The reason this contour was created was because planning was performed using the inverse planning simulation annealing algorithm from Oncentra Brachy Treatment Planning System, version 4.3 (Nucletron an Elekta company, Veenendaal, The Netherlands). Dose was optimized to this CTVopti target followed by manual local graphical optimization. All channels were treated the same, and thus no attempt was made to weigh the central tandem more than any of the more peripheral channels. The median HDR-BT dose was 6 Gy × five fractions (range, 4.75–7 Gy; 4–6 fractions) delivered twice a day during the course of a single implant. In general, dose constraints were to keep the rectal dose to the most irradiated 2cc volume (D_{2cc}) < 70–75 Gy, the sigmoid D_{2cc} to <70–75 Gy, the bladder D_{2cc} to <90 Gy, the dose covering 90% of the target volume (D_{90}) to >100%, and the percentage of CTV receiving 150% of the prescription dose (V_{150}) to <35%. There were no predetermined urethral dose optimization goals. All implants were checked at least once daily with repeat CT simulation, and images were synchronized with the original scans. Catheters were then adjusted to within 5 mm of their original position.

Doses were converted to an equivalent 2-Gy dose (EQD2) based on the linear quadratic equation. An alpha/beta ratio of 3 was assumed for acute reacting tissues, whereas an alpha/beta ratio of 10 was assumed for late tissues.

Clinical outcome definitions

LC was defined as no evidence of disease in the area of the original tumor, as identified by imaging and/or clinical examination at followup. Regional control (RC) was defined as lack of disease progression in the parametria and/or pelvic lymph nodes. Distant metastasis (DM) was defined as the occurrence of disease at a location other than the local or regional sites. Toxicity outcomes were scored using Common Terminology Criteria for Adverse Events, version 4.

Statistical analyses

The Statistical Analysis System (SAS Institute, Cary, North Carolina, USA) computer program was used for the analyses. Kaplan–Meier curves were generated to calculate 2-year actuarial results. All outcomes were calculated from the date of diagnosis. Univariate and multivariate Cox proportional hazards models were run using the Statistical Analysis System, with significance specified as $p < 0.05$. Two-sample Student's t tests assuming unequal variances were used to evaluate the means of survival,