Original Research

Severe Gastrointestinal Complications in the Era of Image-guided High-dose-rate Intracavitary Brachytherapy for Cervical Cancer

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ABSTRACT

Purpose: The purposes of this analysis are to report a modern series of severe gastrointestinal toxic effects after definitive chemoradiotherapy in the treatment of locally advanced cervical cancer at our institution and to review the existing literature on factors that contribute to toxic effects and preventive strategies and management.

Methods: Our institution's cervical cancer cohort was evaluated for patients with late grade 3 to 4 gastrointestinal toxic effects who were retrospectively reviewed for clinical or dosimetric parameters that could have contributed to late toxic effects. A review of the published literature was performed to identify factors associated with late toxic effects, prophylactic agents, and corrective therapy.

Findings: Five of 85 patients were identified as having late grade 3 to 4 gastrointestinal toxic effects with a median follow-up of 13.3 months. Two of 5 patients developed late grade 3 toxic effects, and 3 of 5 developed late grade 4 toxic effects. Three of the 5 patients reviewed ultimately required permanent colostomies. Cumulative median dose (in equivalent dose in 2-Gy fractions) of clinical target volume to the hottest 90% was 107.2 Gy, rectal dose to the hottest 2 cc (D2cc) was 81.7 Gy, sigmoid D2cc was 61.7 Gy, and bladder D2cc was 79.5 Gy. No patient had evidence of disease recurrence in the pelvis. One patient developed oligometastatic disease in the suprarenal gland and was successfully salvaged with adrenalectomy.

Implications: Despite its risk of toxic effects, intracavitary brachytherapy remains a critical component of the treatment of locally advanced cervical cancer. Even with modern radiotherapy planning and delivery techniques, extra attention is warranted to continue to strive for optimal outcomes. (*Clin Ther.* 2015;37:49–60) © 2015 Elsevier HS Journals, Inc. All rights reserved.

Key words: brachytherapy, cervical cancer, gastrointestinal, high dose rate, rectum, toxicity.

INTRODUCTION

Intracavitary brachytherapy has been used in the treatment of cervical cancer since the use of vaginal radium insertions more than a century ago.[1,2] Since that time there have been numerous reports of late gastrointestinal (GI) toxic effects after radiotherapy. In more recent years, there has been a transition from low-dose-rate (LDR) to high-dose-rate (HDR) brachytherapy, with reported similar cancer-specific outcomes and improved safety profiles and logistics of administration with HDR brachytherapy.[3] In addition

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to these changes in brachytherapy delivery approaches, a considerable international effort has been made to improve target coverage and limit dose delivered to adjacent organs at risk (OARs). This effort has largely focused on the adaptation of 3-dimensional (3D) computerized treatment planning with computed tomography (CT) and magnetic resonance imaging (MRI). This approach allows for a more accurate optimization and calculation of dose delivery to target structures and OARs.[4] Although the use of volumetric target optimization during brachytherapy is well described,[5] late GI toxic effects remain a serious risk after definitive radiotherapy.

Our goal is to evaluate the occurrence of severe GI toxic effects after definitive chemoradiotherapy with contemporary image-guided brachytherapy for the treatment of locally advanced cervical cancer at our institution. We also review existing literature on the topic.

REPORT OF INSTITUTIONAL PATIENT OUTCOMES

From a cohort of 85 patients who received definitive chemoradiotherapy for locally advanced cervical cancer during 2011 to 2013, we identified 5 patients who developed late grade 3 to 4 GI toxic effects, as defined by the *Common Terminology Criteria for Adverse Events (CTCAE),* version 4.0.[6] The review was performed with approval from the Institutional Review Board for Health Sciences Research at the University of Virginia. Patient and treatment information was obtained through medical record review. Table I gives the baseline patient characteristics for the 5 patients who developed grade 3 to 4 GI toxic effects. The median follow-up time for the 5 patients who developed late GI toxic effects was 13.3 months. Mean age at presentation was 43.8 years, and mean initial clinical cervical tumor size was 6.5 cm. Patient conditions were staged based on current International Federation of Gynecology and Obstetrics[7] and American Joint Committee on Cancer[8] staging manuals. No patient had a recorded history of diabetes mellitus or a known connective tissue disorder. Four of 5 patients had a history of tobacco use, and 3 smoked tobacco while under treatment.

All patients received external beam radiotherapy (EBRT) concurrent with weekly cisplatin chemotherapy (range, 45–50.4 Gy in 25–30 fractions). Para-aortic nodal basins were included in one patient. At the conclusion of whole pelvic radiotherapy, each patient was given general anesthesia and underwent suturing of a Smit Sleeve into the cervical os before tandem and ovoid applicator placement. Subsequent fractions were performed while the patient was conscious after premedication. For each HDR brachytherapy fraction, patients underwent imaging using an in-room CT on-rails system[9] after applicator insertion, and a new plan was followed for each fraction. An iridium-192 isotope was used in all HDR treatments. All contouring and optimization were performed with BrachyVision treatment planning software (Varian Medical Systems Inc, Palo Alto, California). For each fraction, a dose was prescribed to an isodose line and normalized to point A. Adverse events were graded by the *CTCAE*.[6]

To prevent further delays in total treatment duration, 1 patient received brachytherapy with the twice-daily schedule. Table II reports the cumulative biological effective dose and equivalent dose in 2-Gy fractions (EQD2) to the high-risk clinical target volume (CTV), rectum, sigmoid colon, and bladder. Cumulative doses were calculated under the linear-quadratic equation assuming an α/β ratio of 3 and 10 for OARs and CTV, respectively. In EQD2, the median CTV dose to the hottest 90% (D90%) was 107.2 Gy, rectal dose to the hottest 2 cc (D2cc) was 81.7 Gy, sigmoid D2cc was 61.7 Gy, and bladder D2cc was 79.5 Gy. Patients who received a parametrial or nodal external beam boost did not have boost doses included in these calculations because dose overlap was usually minimal and difficult to accurately predict.

With a median follow-up of 13.3 months, all 5 patients are alive, and no patient has developed recurrent disease within the pelvis. The mean time to hospital admission or surgery from treatment-related toxic effects was 8.8 months. There was no grade 5 toxic effect. One patient developed a metastasis to the right adrenal gland found on 3-month posttreatment positron emission tomography–CT and received salvage surgery with adrenalectomy. She currently has no evidence of disease.

REVIEW OF LITERATURE AND RELEVANCE TO INSTITUTIONAL SERIES

Incidence

Several studies have reported on the incidence of GI complications after definitive radiotherapy and chemoradiotherapy with HDR brachytherapy for cervical cancer, and the reported incidences vary widely from approximately 5% to 30%. This is in

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