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Image-guided tandem and cylinder brachytherapy as monotherapy for definitive treatment of inoperable endometrial carcinoma

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HIGHLIGHTS

- Many women are unable to undergo standard surgical staging for endometrial cancer.
- Women with low-volume disease were treated with 3D-image guided brachytherapy alone.
- Two-year overall and cancer-specific survival rates were 90% and 97%, respectively.
- No grade 3+ acute or late toxicity was observed.
- Brachytherapy is an alternative approach in low-volume disease inoperable women.

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ABSTRACT

Objectives. Management of endometrial cancer consists of surgical staging with adjuvant therapy guided by risk factors, though some women cannot undergo surgery due to comorbidities. We present a series of women treated with definitive high-dose rate image-guided tandem and cylinder brachytherapy (HDR-IGBT) alone.

Methods. Patients with grade 1–2, clinical stage I endometrial adenocarcinoma, <50% myometrial invasion, and tumor ≤2 cm were reviewed. Definitive treatment consisted of 5–6 fractions HDR-IGBT alone with CT- or MRI-based planning. Local-regional control (LRC) was defined as complete imaging response and/or cessation of vaginal bleeding.

Results. From 2007 to 2016, 45 patients were treated to a median dose of 37.5 Gy. The median gross tumor volume (GTV) and clinical target volume (CTV) were 5.9 cm^3 (range, 0.7–18.7) and 80.9 cm^3 (17.2–159.0), respectively. The median cumulative dose to 90% (D90) of the GTV was 132.8 Gy (76.5–295.6) equivalent 2 Gy dose, and the median CTV D90 was 49.7 Gy (34.5–57.2). Median follow-up among living patients was 18.6 months (3.0–64.3). Cessation of vaginal bleeding occurred in 98%. Among those with post-treatment MRI (64%), complete radiographic response was demonstrated in 90%. The 2-year LRC, cancer-specific survival, and overall survival rates were 90%, 86%, and 97%, respectively. No grade 3+ acute or late toxicity was observed.

Conclusions. HDR-IGBT alone for treatment of early-stage, medically inoperable endometrial cancer is feasible with excellent response rates and clinical results. This approach also allows sparing of critical organs and ensures target coverage, which contributed to the low toxicity rate and high LRC in comparison with 2D point-based series.

1. Introduction

Endometrial cancer is the most common gynecologic malignancy in the U.S. with an estimated 61,380 diagnoses and 10,920 deaths in 2017 [1]. Rising incidence is related in part to the growing elderly population and a concomitant increase in obesity rates, both of which trends are anticipated to continue in the coming years [2,3]. Standard of care management of newly diagnosed endometrial cancer involves surgical staging including total abdominal hysterectomy with bilateral salpingo-oophorectomy with or without pelvic and para-aortic lymph node evaluation. Adjuvant therapy may consist of some combination of pelvic radiation therapy (PRT), vaginal brachytherapy (BT), or systemic therapy, depending upon baseline patient risk factors and pathologic findings [4–6].

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Considering that advanced age and obesity are prominent risk factors for endometrial carcinoma, a significant proportion of patients will present with medical comorbidities precluding definitive surgical management, which has been estimated to comprise between 4 and 9% of presenting patients [7,8]. Definitive RT has been the mainstay of treatment in this population. Institutional series have reported loco-regional control rates for clinical stage I disease ranging from 71 to 92% with combination PRT and BT, though overall survival rates are typically poor due to the medical frailty of these patients [8–15]. Despite excellent outcome data, a recent systematic analysis found that 39% of medically inoperable patients do not receive any definitive therapy [16].

BT is an integral component of treatment in medically inoperable patients, confirmed to improve survival compared with PRT alone through a hospital-based registry analysis [17]. In select patients with low volume, early stage disease, BT alone has been shown to provide adequate loco-regional control while sparing the added toxicity of PRT. Most historical series have included patients treated with two-dimensional (2D) point-based dosimetry, and have reported late grade 3 or higher toxicity rates ranging from 5 to 21% [18–21]. In recent years, three-dimensional (3D) image-guided BT (IGBT) techniques have been developed for treatment of gynecologic malignancies and have been shown to improve local control rates and reduce toxicity due to the ability to deliver a conformal RT dose to the target while decreasing dose to nearby organs-at-risk (OAR) [22–24]. We present clinical outcomes of a series of patients treated with definitive high-dose-rate (HDR) 3D-IGBT as monotherapy for low grade, early stage inoperable endometrial cancer.

2. Materials and methods

2.1. Patient population

We retrospectively reviewed patients with clinical stage I medically inoperable endometrial cancer treated with definitive HDR 3D-IGBT as monotherapy at UPMC Magee-Womens Hospital from November 2007 to October 2016. Staging workup included clinical examination and the use of imaging modalities including CT and/or MRI. MRI was obtained due to better negative predictive value for ruling out deep myometrial invasion (MMI) except when contraindicated due to factors such as patient body habitus, claustrophobia, or the presence of incompatible pacemakers [25]. When MRI was contraindicated, PET-CT was obtained for better delineation of disease beginning in 2013. Patients were selected for 3D-IGBT as monotherapy if they had tumors with grade 1–2 histology and low-volume disease defined as <50% MMI and tumor size ≤2 cm on MRI and a maximum uterine width of 5 cm. Patients receiving systemic hormonal therapy such as megestrol acetate or having placement of levonorgestrel intrauterine device (IUD) prior to brachytherapy were not included.

2.2. Treatment

An MR-compatible Smit Sleeve (Nucletron, Elekta AB, Stockholm, Sweden) was placed in the operating room prior to initiation of BT. BT treatment consisted of 5–6 fractions of HDR 3D-IGBT delivered twice weekly utilizing a tandem and cylinder applicator. Appropriate tandem length was selected based on uterine sound at time of Smit Sleeve placement and with ultrasound confirmation of tandem placement at time of applicator placement. Clinical examination was performed to estimate the vaginal vault width, and the largest fitting cylinder diameter, ranging from 2.5 to 3.5 cm, was selected. At our institution, the Rotte "Y" applicator is generally utilized in patients with a maximum uterus width >5 cm. This study included patients with uterine width 5 cm or less, though if patients are unable to lie flat for a prolonged period of time as required for the "Y" applicator, then they were treated with a tandem and cylinder. A total of 12 patients (27%) with uterine width >5 cm were included in this analysis. Patients treated with a Rotte "Y" applicator were not included in this analysis. Applicator placement was performed either under conscious sedation or with analgesic medications depending upon the patient's comfort and ability to tolerate the procedure. Either a CT scan or MRI was obtained with the applicator in place prior to each fraction. Planning imaging was categorized as CT-based plans alone, CT-based plans with MRI obtained prior to BT (MRI-guided), and MRI-based plans with MRI obtained with applicator in place (MRI-based). Utilization of MRI was preferred to accurately delineate the target volumes and critical OAR except in cases where MRI was contraindicated.

In all cases, the dose was prescribed to the clinical target volume (CTV), which consisted of the entire uterus, cervix, and upper 1–2 cm of the vagina [26]. For patients who underwent MRI-based or MRI-guided planning, the gross tumor volume (GTV) was defined as any visible abnormality on T2-weighted images. When MRI or PET-CT were unavailable, the dose was prescribed the CTV alone. BT doses were calculated and normalized to the equivalent 2 Gy dose (EQD_2). The typical absolute prescription dose ranged from 7 to 7.5 Gy per fraction with a goal of delivering ≥48 Gy EQD2 to the CTV and ≥80 Gy to the GTV. OAR were delineated including the sigmoid colon, rectum, bladder, and small bowel. Treatment plans were generated using either the PLATO Brachytherapy Planning System, version 4.3 (Nucletron) or, later in the series, the Oncentra Brachy Planning System, version 4.3 (Elekta). Standard weighting was initially placed at each source position and then manually adjusted to adequately cover the CTV while avoiding critical structures. The doses to $2cm^3$ of organs-at-risk were constrained to receive less than the CTV prescription dose, and no portion of the OAR was to receive >100% of the prescription dose. An example treatment plan demonstrating target and organ-at-risk contouring in axial and sagittal views is included in Fig. 1. The dose to 90% (D_{90}) of the CTV and GTV were recorded, as well as the maximum dose to 2 cm^3 (D_{2cm^3}) for surrounding OARs.

2.3. Outcome analysis

Follow-up examinations included a routine history and physical examination with pelvic examination, cervical cytology, and imaging including an MRI when possible. Radiographic response was determined based upon residual signal abnormality within the uterus and categorized as complete response, residual signal abnormality, or disease progression. Serial follow-up imaging was performed in cases of apparent residual disease to allow for continued disease regression. Local-regional control (LRC) was defined as complete imaging response and/or cessation of vaginal bleeding if post-treatment MRI was unavailable. Histologic confirmation was performed for any suspicious imaging findings to rule out local failures or persistence of disease. Overall survival (OS) was defined as date of completion of brachytherapy to last follow-up to date of death from any cause. Toxicity was retrospectively graded using the Common Terminology Criteria for Adverse Events, version 4. Kaplan-Meier analyses were performed to estimate rates of loco-regional control and overall survival. All statistical analyses were performed using SPSS version 24 (IBM Corp., Armonk, New York).

3. Results

3.1. Patient and treatment characteristics

From 2007 to 2016, 45 consecutive women underwent definitive BT alone for treatment of medically inoperable endometrial cancer. Forty-three patients (96%) had clinical stage I disease. Two (4%) patients had demonstrated endometrial nodularity on imaging but only complex atypical hyperplasia was demonstrated on endometrial biopsy. This was felt to be sampling error based upon a mass demonstrated on MRI, and so these 2 patients were included in the analysis. The most common reasons for inoperability included multiple medical comorbidities (64%), morbid obesity (16%), and need for anticoagulation (16%). One patient (2%) with grade 3 disease was treated with BT alone due

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