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Hybrid Arc Stereotactic Ablative Body Radiation Therapy for Pelvic Relapse of Gynecologic Malignancies

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Abstract

Relapsed gynecologic cancers are difficult to control in the pelvis, especially when surgery, chemotherapy and radiation treatments have already been administered. For this clinical scenario, stereotactic body radiation therapy has emerged as a meaningful treatment strategy. The new Vero stereotactic body radiation therapy system uses coplanar and noncoplanar radiation treatment beams with submillimeter precision to treat cancer targets. This study describes the initial clinical experience with Vero hybrid arc stereotactic ablative body radiation therapy to treat relapsed gynecologic cancers detected in the pelvis.

Keywords

Vero, Radiosurgery, Stereotactic body radiation, Hybrid arc, Cervical cancer, Endometrial cancer

Introduction

Bulky pelvic relapses of gynecologic cancers might produce foul-smelling vaginal secretions and bleeding, pelvic pain, dysuria, or bowel obstruction [1]. Clinical management of these symptoms remains a challenge without control of the pelvic disease, especially when considering its proximity to the bowel and the bladder. Moreover, previous surgical and chemotherapy assertiveness and any prior pelvic radiation dose confound management of bulky pelvic relapses after primary cancer intervention [1].

One method of controlling relapsed gynecologic cancer in the pelvis is a potentially morbid surgery, the so-named pelvic exenteration [2,3]. For patients that would otherwise require exenteration, stereotactic ablative body radiation therapy (SBRT) has emerged as a non-invasive precise radiation treatment. In a phase II clinical trial, robotic SBRT demonstrated a 96 percent abdominopelvic disease target control rate without undo normal organ injury [4]. Robotic SBRT involved image-guided "pencil beam-sized" radiation beams delivering a hypofractionated radiation dose (8Gy X 3 consecutive daily fractions) [4]. Modern SBRT delivery systems mount a clinical radiation accelerator either to an industrial robotic arm [5], or to a helical slice-by-slice gantry [6], or within a conventional machine but have it driven by image-guided intensity modulated radiation therapy or dynamic arc delivery software [7]. Recently, a first-in-class SBRT delivery system has come to market, the Vero SBRT system [8-10].

The Vero SBRT system uses a gimbaled (±4cm) pan-and-tilt radiation accelerator, whose sixty 110-millimeter tall tungsten alloy leaves fashion a radiation beam for a very narrow radiation field penumbra. Dual-diagnostic Exactrac kV x-ray units and an infrared camera unit allow for 'between-beam' feedback of cancer target abdominopelvic motion. A robotic pivoting O-ring (±60°) and rotational gantry (±185°) permit coplanar and non-coplanar unique treatment degrees of freedom for static and rotational arc radiation beams. In spite of all of these mechanical manipulations, Vero SBRT has submillimeter isocenter accuracy (0.4mm) [11]. No prior studies describe Vero hybrid arc SBRT to treat relapsed gynecologic cancers in the pelvis. Here, we report the initial case series experience.

Materials and Methods

Stereotactic ablative body radiation therapy

Between November 2014 and January 2015, three consecutive patients underwent hybrid arc SBRT using the Vero SBRT platform (Brainlab, Inc., Munich, Germany; Mitsubishi Heavy Industries Ltd., Tokyo, Japan) for treatment of gynecologic cancer relapses occurring in the pelvis not amenable to surgical or conventional radiation intervention. All patients underwent therapy at Summa Health System Akron City Hospital (Akron, Ohio, USA). With permission from the Summa Health System institutional review board, we conducted a retrospective case series analysis of Vero hybrid arc stereotactic body radiation therapy applied to the pelvis.

After consultation discussing surgical and non-surgical palliative treatment strategies, all three patients elected and consented to Vero stereotactic body radiation therapy. Patients underwent one to three gold-coated metallic fiducial marker placement within or around relapsed pelvic cancer targets [1]. Patients then had supine computed tomography (CT) scans with two-pin localizing, pelvic immobilization. Images were acquired as a non-contrasted contiguous helical axial CT scan with three-millimeter slice thickness (voltage 120kVp, 350mAs) and were transferred to the iPlan treatment planning system (Brainlab, Inc.). 2-[^{18}F] fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography (PET) images if any were obtained per institutional routine and were transferred into the planning system for enhanced tumor target contouring similar to previous experience [12]. The treating radiation oncologist contoured the relapsed pelvic cancer targets and occult at-risk tissue,

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Figure 1: The Vero SBRT system

labeled as the clinical target volume (CTV). If acquired, a thresholded 40 percent maximum standard uptake value contour on the ^{18}F-FDG PET images created an PET clinical target volume (CTVpet) [12]. If a CTV and a CTVpet were contoured, then both volumes were combined into a single composite volume (CTV+CTVpet). The CTV or CTV+CTVpet volumes were expanded uniformly by five millimeters to generate a planning tumor volume (PTV). Normal tissue small bowel, rectum, bladder, bilateral kidneys, bilateral proximal femurs, and sacral foraminae (as surrogates for nerve root paths) were contoured most often for radiation dosimetry planning. Vero hybrid arc stereotactic body radiation therapy (Figure 1) was prescribed as 8 Gy per fraction for three fractions [4].

Prior to radiation delivery, the treating radiation therapists verified gantry rotation and O-ring pivot position clearance of the patients. During Vero hybrid arc stereotactic body radiation therapy delivery, the treating radiation oncologist verified positional accuracy of soft tissue fiducial markers (i.e., the relapsed pelvic cancer target) using cross-plane Exactrac kV x-ray prior to any beam arc or static beam.

Toxicity assessments

Toxicity was assessed prior to therapy on the first day of treatment, the last day of treatment, and four weeks after treatment. Toxicity was graded following National Cancer Institute common terminology criteria for adverse events (CTCAE) version 4. For this study, toxicity data was compiled retrospectively at chart review.

Results

Case reports

Case 1: A 67-year-old gravida 0, para 0 woman diagnosed with FIGO stage IB, grade 1 endometrioid adenocarcinoma of the uterus underwent definitive four-field pelvic radiation to a total dose of 50.4Gy in 28 fractions in June 2009. A single brachytherapy application of 6.3Gy was delivered in July 2009. No surgery was done. She had no clinical evidence of disease for 5 years, but had lingering back pain requiring anti-inflammatory and opioid pain management.

In November 2014, she developed a 5cm non-operable central vaginal apex mass intimately associated with the rectum and fixed to the pelvic floor. Interstitial brachytherapy was not technically feasible given the close proximity of her relapsed mass and rectum. Surgical resection was not advised given adherence of the relapsed mass to the pelvic floor and given the associated surgical morbidity risk. Given her desire for treatment and a recommendation for stereotactic body radiation therapy from a gynecologic oncology tumor board, she elected and consented to SBRT treatment in late November 2014. After written informed consent, she had one gold-coated fiducial marker placed by the treating radiation oncologist within the relapsed vaginal apex mass under 2% topical lidocaine anesthesia. Non-contrasted computed tomography simulation was done seven days afterward. The patient was unable to tolerate an ^{18}F-FDG PET scan in a protracted supine position.

A PTV of 257cm^3 received 24 Gy in three fractions of 8Gy prescribed to the 100% isodose line with a conformality index of 1.04 to achieve 95% target coverage. Two non-coplanar hybrid dynamic arc searches with seven integrated 6MV intensity modulated radiation therapy static photon beams were used. Fiducial marker tracking was done each before the arc and before the static field group. During her fractionated SBRT course, she developed no significant skin, urinary, or gastrointestinal toxicities. At four-week follow-up, she had no pelvic bleeding, pelvic pain, or other symptomatic complaints.

She remains alive three months after Vero hybrid arc stereotactic body radiation therapy without symptoms or clinical pelvic disease progression.

Case 2: A 66-year old gravida 2, para 2 woman had a stage IB, grade 2 endometrioid adenocarcinoma of the uterus diagnosed in September 2012. She underwent laparoscopic-assisted total hysterectomy and bilateral salpingo-oophorectomy with lymph node sampling in October 2012. Intravaginal brachytherapy was administered to the proximal four centimeters of the vagina for a dose of 21Gy in three weekly fractions. She completed therapy in December 2012.

In June 2014, she had recurrent disease detected in the left (5 centimeters) and right (2 centimeters) vaginal apices on pelvic examination and CT imaging. Rather than pelvic exenteration, she elected palliative four-field pelvic radiation and completed a course of 45Gy in 25 fractions in July 2014. Post therapy surveillance pelvic examination and CT imaging confirmed a partial response to therapy in December 2014.

At this time, a treatment recommendation for SBRT was made and agreed at a gynecologic oncology tumor board. Palliative treatment options were presented to the patient in December 2014. She agreed to the recommended SBRT treatment and signed informed consent. She had single fiducial markers placed by the treating radiation oncologist into each of the two vaginal masses under 2% topical lidocaine anesthesias in December 2014. Non-contrasted computed tomography simulation was done two days after fiducial marker placement.

A PTV of 255cm^3 received 24Gy in three fractions of 8Gy prescribed to the 100% isodose line with a conformality index of 1.06. Ninety percent PTV target coverage was achieved. One hybrid dynamic arc with seven integrated 6MV intensity modulated radiation therapy static photon beams were utilized in the radiation plan. Fiducial marking tracking was done before the arc and before the static field group. Over her SBRT course, she complained of no skin, urinary, or gastrointestinal adverse events. At her four-week follow-up, she reported grade 2 fatigue and a urinary tract infection, both of which did not limit her activities.

She remains alive three months after Vero hybrid arc stereotactic body radiation therapy. Her cancer therapy treatment plan with her gynecologic oncologist includes consideration of post-SBRT systemic chemotherapy.

Case 3: A 34-year old gravida 1, para 1 woman had a stage IB1, grade 2 adenocarcinoma of the uterine cervix first diagnosed in June 2012. She underwent robotic-assisted total hysterectomy and bilateral salpingo-oophorectomy with lymph node sampling in August 2012. Specimen histopathology identified a two-centimeter adenocarcinoma with deep stromal invasion and lymphovascular invasion. Surgical margins were negative. Thirty-four pelvic and low para-aortic lymph nodes were negative for malignancy. She underwent adjuvant intensity modulated radiation therapy to the pelvis to a total dose of 46.8Gy in 27 fractions. No brachytherapy was administered. She completed radiation therapy in January 2013.

In February 2014, she had recurrent disease detected in the right vaginal apex on pelvic examination. Rather than undergo pelvic

exenteration, she elected to receive multiple cycles of bevacizumab, cisplatin, and paclitaxel chemotherapy. Post-chemotherapy surveillance pelvic examination and imaging confirmed a near complete response in July 2014. In December 2014, surveillance ^{18}F-FDG PET scan detected a four-centimeter right pelvic sidewall mass encasing the right ureter (SUV maximum 14). A treatment recommendation for stereotactic body radiation therapy was made the same month at a multidisciplinary gynecologic oncology tumor board. Palliative treatment options were presented to the patient in late December 2014. She agreed to therapy and signed informed consent for SBRT. An interventional radiologist placed three fiducial markers within the right pelvic sidewall mass in late December 2014. Non-contrasted computed tomography simulation was done two days after fiducial marker placement. Her already acquired surveillance ^{18}F-FDG PET scan was overlaid on simulation images for SBRT dosimetry planning.

A tumor volume of 84cm^3 received 24Gy in three fractions of 8Gy prescribed to the 100% isodose line with a conformality index of 1.25. 95% target coverage was reached. One hybrid dynamic arc and seven integrated 6MV intensity modulated radiation therapy static photon beams were applied. Before the arc and before the static field groups, fiducial marker positions were checked. By her second fraction of SBRT, she noted 4/10 pain intensity in the deep right pelvis. Dexamethasone and oxycodone were prescribed, with relief of symptoms noted afterward.

At her four-week follow-up visit, she reported no fatigue or pelvic pain. Surveillance ^{18}F-FDG PET scan done at that time identified improved signal in the pelvic cancer target, but also new disease progression in the liver. She remains alive and her cancer therapy treatment plan with her gynecologic oncologist includes consideration of post-SBRT systemic chemotherapy.

Discussion

For gynecologic cancers initially managed by surgery, chemotherapy, or pelvic radiation, interventions for pelvic relapses pose increase risk of long-term morbidity, such as debilitating lymphedema, diverting colostomy and urinary conduits, and poor body image and sexual health [13-15]. While a small volume isolated central pelvic relapse may be approached surgically, often a pelvic exenteration must be done to remove disease with adequate surgical margin. Patients with co-morbid disease may be unwilling or may be unable to undergo second surgeries for relapsed gynecologic cancers involving the pelvis. Stereotactic ablative body radiation therapy such as that provided by the Vero SBRT system offers treatment with high radiation dose precision and limited therapy-related toxicities.

A phase II clinical trial of robotic-arm SBRT established the safety and efficacy of this approach among patients with relapsed gynecologic cancers [4]. To our knowledge, this case series reports the first experiences of hypofractionated (8Gy X three fractions) Vero hybrid arc stereotactic body radiation therapy in patients with relapsed gynecologic cancers.

In our retrospective case series, delivered radiation was well-tolerated. Corticosteroid and narcotic analgesia alleviated on-treatment pelvic pain in one patient. This symptomatic pain resolved by the four-week follow-up visit. No radiation cystitis or enteritis was encountered during the limited post therapy observation period. Previously determined SBRT planning parameters were rigorously followed [16,17], and may account for the low incidence of toxicity seen in these three patients. Possible late toxicities such as fistula formation or chronic enteritis have not been observed, but follow-up is too premature to comment definitely on the incidence of late Vero SBRT treatment toxicities.

While the phase II clinical trial prescription dose has been carried forward to the Vero SBRT system, Vero hybrid arc stereotactic body radiation therapy results in at least one outstanding treatment difference. Currently, the more widely available robotic-arm platform uses a fixed or iris-collimated linear accelerator that may target only a fraction of the entire intended tumor volume at any single treatment node. This raises the possibility of low marginal radiation dose and geographical miss, as seen early on with robotic-arm stereotactic radiation therapy in the pelvis [1,18]. Later experience demonstrated improved radio surgical target delineation with ^{18}F-FDG PET scan data applied during stereotactic body radiation therapy planning [4,12]. While ^{18}F-FDG PET scan data has been integrated to improve target delineation, Vero hybrid arc stereotactic body radiation therapy treats the entire PTV when the radiation beam is on. We speculate that Vero hybrid arc stereotactic body radiation therapy, refined by ^{18}F-FDG PET scan data, lowers the chance of peripheral cancer cells receiving insufficient radiation prescription dose. Further follow-up of patients with relapsed gynecologic cancers treated by Vero SBRT must be done to validate such a claim.

Overall, these cases indicated that a Vero hybrid arc stereotactic body radiation therapy approach safely delivered radiation dose to abdominopelvic sites of relapsed gynecologic cancers. The therapy may be administered with minimal toxicity even in a group of pretreated patients. The case series would be strengthened by an appraisal of a larger patient cohort, by longer-term follow-up for assessment of treatment-related sequelae and durability of radiosurgical target response, and by reporting of longer-term cancer-related survival outcome.

Conclusion

Vero hybrid arc stereotactic body radiation therapy was safe to deliver, well-tolerated, and provided clinical benefit in the relief of relapsed gynecologic cancer-related symptoms. A prospective clinical trial of Vero hybrid arc stereotactic body radiation therapy in patients with relapsed gynecologic cancers in the abdomen and pelvis would be of clinical interest.

Ethics Statement

This case review study was performed with permission from the Summa Health System institutional review board.

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