Preserving Endocrine Function in Premenopausal Women Undergoing Whole Pelvis Radiation for Cervical Cancer

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Abstract

Purpose: Whole pelvis radiation therapy (WPRT) in premenopausal women with cervical cancer can cause permanent ovarian damage, resulting in premature menopause. Oophoropexy, often considered as an initial step, demonstrates safety of sparing 1 ovary at the cost of delay in initiating WPRT. Therefore, we dosimetrically compared volumetric modulated arc radiotherapy (VMAT) and intensity modulated proton therapy (IMPT) techniques to allow for ovarian-sparing WPRT.

Materials and Methods: Ten patients previously treated for cervical cancer at our institution were included in this institutional review board–approved analysis. A modified clinical treatment volume (CTV) was designed, sparing 1 ovary (left or right), as determined by the physician (ovarian-sparing CTV) and disease extent, including physical exam, positron emission tomography/computed tomography and magnetic resonance imaging. An ovarian-sparing planning target volume was determined as the ovarian-sparing CTV + 5 mm for patients who were supine and 7 mm for those who were prone. All plans were calculated to a dose of 45 Gy with specific optimization goals for target volumes, while attempting to maintain a mean ovary dose ($D_{mean}$), $\leq$ 15 Gy. Dosimetric goals were compared across the 2 modalities using the Mann-Whitney U test.

Results: Both treatment modalities were able to achieve primary clinical goal coverage to the uterus/cervix ($P = .529$, comparing VMAT versus IMPT), ovarian-sparing CTV ($P = .796$) and ovarian-sparing planning target volume ($P = .004$). All 10 IMPT plans were able to accomplish the ovary objective ($14.0 \pm 1.66$ Gy). However, only 4 of the 10 VMAT plans were able to achieve a $D_{mean} < 15$ Gy to the prioritized ovary, with an average dose of 15.3 $\pm$ 4.10 Gy.

Conclusion: Sparing an ovary in women undergoing WPRT for cervical cancer is dosimetrically feasible with IMPT without sacrificing coverage to important clinical targets. Future work will incorporate the brachytherapy dose to the ovarian-sparing CTV and assess the clinical response of this technique as a means to preserve ovarian endocrine function.

Keywords: ovarian cancer; endocrine preservation; intensity modulated proton therapy; pencil beam scanning
Introduction

Cervical cancer remains fairly common in the United States, with a reported 13,240 estimated new cases in 2018 [1]. For locally advanced disease, whole pelvis radiation therapy (WPRT) with brachytherapy remains absolutely necessary for cure [2–4]. However, because of radiation treatment, premenopausal women often experience permanent ovarian endocrine dysfunction, which can result in quality-of-life-altering symptoms such as hot flashes, mood changes, fatigue and sexual dysfunction [5]. Ovarian transposition is a way to preserve ovarian function in gynecologic malignancies [6], but, due to logistics, this can lead to a delay in initiating therapy, which can result in inferior clinical outcomes [7] and increasing cost of care. Although done laparoscopically, it is ultimately an invasive procedure that comes with risks and a reported 35% failure rate in preserving ovarian function [8]. Furthermore, ovarian transposition occasionally fails as the transposed ovary can fall back into the pelvis before initiation of pelvic radiation therapy or during treatment.

A few dosimetric studies have depicted the superiority of intensity modulated proton therapy (IMPT) compared with more advanced photon techniques (ie, intensity modulated radiation therapy [IMRT] or volumetric modulated arc radiotherapy [VMAT]) in decreasing integral dose to important organs at risk (OARs), such as bladder, bowel, bone marrow, and femoral heads in patients with gynecologic malignancies [9–11]. However, no studies have investigated the feasibility of ovarian-sparing WPRT in an effort to preserve endocrine in young women with cervical cancer. We therefore compared the ability of VMAT versus IMPT methods in sparing 1 ovary to a mean dose of 15 Gy or less [12–14] without compromising clinical target coverage in premenopausal women with cervical cancer who did not undergo ovarian transposition before radiation therapy. Although ovarian dose constraints would have to be uniquely selected for clinical practicality depending on patient age at diagnosis, for this feasibility study, the ovarian constraint of 15 Gy was selected as a conservative estimate extrapolated from ovarian-ablation studies done for breast cancer therapy [12, 13]

Materials and Methods

Pretreatment Evaluation

All patients presented in this study were evaluated by a multidisciplinary team, including surgical oncologists, medical oncologists, and radiation oncologists at initial presentation. Patients underwent standard workup, including examination under anesthesia, biopsy with pathology review, and systemic imaging for locally advanced disease (positron emission tomography [PET], PET/computed tomography [CT], CT scans, or magnetic resonance imaging [MRI]). Patients were staged according to the American Joint Committee on Cancer staging criteria (AJCC) 7th edition and did not undergo ovarian transposition before therapy. In younger, premenopausal women, a conversation regarding ovarian transposition was documented and not performed based on a consensus from both the patient and provider.

Clinical Target and Radiation Delivery

Patients underwent contrast or noncontrast CT simulation scans and were immobilized in the supine or prone position with a comfortably full bladder. Ovarian-sparing clinical target volumes (CTVs) were delineated by a single physician using both CT and MRI images, where an ovary (left or right) was chosen for avoidance. A board-certified, gynecologic-focused radiologist confirmed the accuracy of ovary delineations. The target volume CTV included common iliac, internal and external iliac vessels, the presacral space, the entire uterus/cervix, the parametrium, the upper half of the vagina, and gross tumor as seen on physical exam and imaging studies. The CTV also included an internal target volume (ITV) for uterus/cervix movement, which was generated using an empty and full bladder on CT simulation scans [15]. The ovarian-sparing CTV was generated by creating a 10-mm expansion from the prespecified ovary (ovary ITV) and subtracting it from the target CTV as previously described, thereby ensuring that the cervix/uterus was still covered. A planning target volume (PTV) was created using a 5-mm and 7-mm expansion from the ovarian-sparing CTV if patients were supine or prone, respectively. A planning organ-at-risk volume was also created (range: 5–7 mm) for the avoidance ovary to assist with dosimetric achievement clinical goals.

Patients were typically treated with 3-dimensional conformal radiation therapy; however, for the purposes of this study, VMAT and IMPT plans were created using RayStation (version 6.1.1.2; RaySearch Laboratories, Stockholm, Sweden). The VMAT plans were generated using a single isocenter with 6 MV photons and 2 full arcs. Comparison IMPT plans used a proton scanning pencil beam with a nominal spot size (sigma in air) of 4 mm with beam energies selected by the treatment planning software (available range: 70–245 MeV). Multifield optimized plans were created for this analysis, using 2 lateral fields (90° and
270°) and a posterior beam for radiation delivery (Figure 1). All IMPT plans were robustly optimized to account for a setup error (5 mm for supine and 7 mm for prone positions) and a proton range uncertainty of 3.5%.

**Evaluation Tools**

All whole-pelvis plans were prescribed a dose of 45 Gy delivered in 1.8 Gy per fraction, and plan evaluations were based on analysis of dose-volume histogram (DVH) parameters. Clinical goals for the ovarian-sparing CTV was a V45 (volume receiving at least 45 Gy) of 98% and a V45 of 95% for the ovarian-sparing PTV. The V45 to the cervix/uterus was set at 99% to 100%. The mean dose to the avoidance ovary (Dmean) was optimized to be <15 Gy only if previous dosimetric goals were not compromised. The volume of the prioritized ovary receiving 7.5 Gy was also reported [16]. An acceptable worst-case scenario IMPT plan robustness was defined as a D95 (dose delivered to 95% of the ovarian-sparing CTV) greater than or equal to 85% to 90% of the prescribed dose. Hot spots were limited to <110% of the prescribed dose.

The dose to other OARs were also compared between the 2 techniques, including the V10, V20, V30, V40, and maximum dose to small bowel and femoral heads; the V10, V20, V30, V40, and D2cc dose (maximum dose to 2 cc² of organ) to bladder and rectum; and the V10, V20, and V40 to the pelvic bone marrow. The Mann-Whitney U test was used to compare the aforementioned DVH values between IMPT and VMAT plans for each patient, where a 2-sided P value <.05 was considered statistically significant. Statistical analyses were performed using SPSS software (version 23.0; IBM Corp, Armonk, New York).

**Results**

**Clinical Target and Optimized Ovary DVH Analysis**

Both VMAT and IMPT plans were able to meet clinical target coverage as summarized in the Table. Proton plan robustness was clinically acceptable in all 10 cases, where the worst-case scenario was >98% of the prescription dose covering 95% of
the ovarian-sparing CTV. Dose to the uterus/cervix ($P = .529$) and to the ovarian-sparing CTV ($P = .796$) was indistinguishable between the 2 methods (Figure 2A). Although dose coverage to the ovarian-sparing PTV was superior in the photon group ($P = .004$), all of the proton therapy plans met the primary PTV clinical objective with a mean $D_{\text{mean}}$ of 95.23% ± 0.73% (Table). All 10 IMPT plans were able to achieve a mean prioritized ovary dose $< 15$ Gy (14.02 ± 1.66 Gy), whereas only 4 of the 10 VMAT plans were successful (15.30 ± 4.10 Gy) (Figure 2B). The volume of the prioritized ovary receiving 7.5 Gy or higher was significantly greater with VMAT compared with IMPT (Table; $P = .011$).

**DVH Analysis of Other OARs**

The DVH analyses for other OARs are summarized in supplemental Table 1 and Table 2 for VMAT and IMPT plans, respectively. Proton therapy techniques have statistically superior sparing of low dose to the small bowel (Figure 3A; mean percentages of OAR seeing at least 10 Gy and 20 Gy for VMAT were $V_{10} = 72.48\% \pm 20.62\%$ and $V_{20} = 6.60\% \pm 18.59\%$ and for IMPT were $V_{10} = 43.65\% \pm 17.06\%$ and $V_{20} = 28.33\% \pm 13.08\%$), bladder (Figure 3B; VMAT: $V_{10} = 100.00\% \pm 0.01\%$) and the ovarian-sparing CTV. Dose to the uterus/cervix ($P = .529$) and to the ovarian-sparing CTV ($P = .796$) was indistinguishable between the 2 methods (Figure 2A). Although dose coverage to the ovarian-sparing PTV was superior in the photon group ($P = .004$), all of the proton therapy plans met the primary PTV clinical objective with a mean $D_{\text{mean}}$ of 95.23% ± 0.73% (Table). All 10 IMPT plans were able to achieve a mean prioritized ovary dose $< 15$ Gy (14.02 ± 1.66 Gy), whereas only 4 of the 10 VMAT plans were successful (15.30 ± 4.10 Gy) (Figure 2B). The volume of the prioritized ovary receiving 7.5 Gy or higher was significantly greater with VMAT compared with IMPT (Table; $P = .011$).

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and $V_{20} = 93.40\% \pm 9.11\%$; IMPT: $V_{10} = 93.16\% \pm 10.00\%$ and $V_{20} = 81.16\% \pm 11.38\%$), and bone marrow (Figure 3C; VMAT: $V_{10} = 94.62\% \pm 4.07\%$ and $V_{20} = 76.90\% \pm 7.96\%$; IMPT: $V_{10} = 79.0\% \pm 8.97\%$ and $V_{20} = 52.57\% \pm 9.84\%$). The $V_{30}$ and $V_{40}$ to the small bowel ($V_{30}: P = .436; V_{40}: P = .912$), bladder ($V_{30}: P = .393; V_{40}: P = .853$) and bone marrow ($V_{40}: P = .353$) were similar between the 2 methods. There was no difference in any of the dose parameters for the bilateral femoral heads ($V_{10}: P = .739; V_{20}: P = .639; V_{30}: P = .481; V_{40}: P = .089$) or rectum, save for the $V_{20}$ ($V_{10}: P = .143; V_{20}: P = .023; V_{30}: P = .315; V_{40}: P = .853$) when comparing techniques.

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Discussion

In this dosimetric feasibility study, we have demonstrated the ability to consistently spare a prioritized ovary to a mean dose of 15 Gy in women with cervical cancer planned for WPRT with IMPT, while maintaining adequate coverage to other clinical targets (Table). Our prioritized ovary constraint in this analysis stems from the breast cancer literature, where ovarian ablation using a dose of approximately 20 Gy given in conventional fractionation results in 70% to 90% induction of amenorrhea [12–14, 17]. Thus, we wanted to be conservative with the use of 15 Gy in this analysis since ovarian function is highly dependent on age, where older (>30 years) premenopausal women are more sensitive to lower doses of radiation [18]. In reality, ovarian dose constraints used in the clinical setting would have to be uniquely adjusted based on the patient's age at time of treatment, where using a dose constraint as low as 7 Gy may be necessary in some women older than 40 years [16, 18]. Furthermore, chemotherapy itself can cause endocrine dysfunction in premenopausal women undergoing definitive therapy, and though alkylating agents are often the culprits [19], the use of platinum-based chemotherapy must also be accounted for when determining patient-specific ovarian constraints.

In creating our ovarian-sparing CTV, we applied a 10 mm margin on the prioritized ovary, which we felt was a fair compromise between ensuring that we had good coverage on important clinical targets (ie, uterus/cervix, lymphatic sites) and accounting for ovarian motion [20]. An additional 5–7 mm margin was also created for generating the PTV. An MRI study done by Peters et al [20] noted that a “safety volume” of 11 cm³ and 25 cm³ was necessary to encompass 95% of the left and right ovarian motion, respectively. These volumes correspond to an approximate 2.2 to 2.8 cm expansion for the prioritized ovary.

For clinical efficacy, we would most likely use daily cone beam computed tomography image guidance as available in modern proton centers to ensure ovary position during therapy, as creating larger PTVs might compromise important target coverage, such as the uterus and adjacent lymphatic areas. This being the case, the eligibility criteria for future clinical practicality would most likely be limited to premenopausal women with early stage (ie, FIGO [Fédération Internationale de Gynécologie et d’Obstétrique] stage I or II) disease, with no evidence of pelvic adenopathy. Nevertheless, we are confident in proceeding to clinical feasibility given that the ovary is rarely ever a site of cervical cancer metastasis as noted from the ovarian transposition literature [8].

Ovarian transposition is a surgical technique that has been used as a means to preserve endocrine function since the late 1950s [21], and though the procedure has become minimally invasive, it can delay definitive treatment, which can negatively affect outcomes [7] while increasing the financial burdens of oncologic care. Consequently, the focus of our study was on women who did not undergo oophoropexy. We compared modern photon techniques using VMAT to IMPT, and though the mean prioritized ovary dose was not statistically significantly different between the 2 methods, IMPT was able to reliably achieve our goal in all 10 treatment plans. Interestingly, 3 of the 4 VMAT plans that were able to attain an ovary Dmean < 15 Gy were patients in the prone position (Table), which suggests that this method can possibly be adopted for patients who can tolerate the position. Additionally, proton therapy was able to significantly spare integral low dose to the prioritized ovary (V7.5; Table) over VMAT, which has been correlated to ovarian function in a small retrospective study in young women with cervical cancer who have undergone hysterectomies and required postoperative radiation therapy due to high-risk disease [16].

Previous studies have also shown the dosimetric advantage of IMPT in gynecologic malignancies over modern photon techniques, with improved sparing of various OARs, such as small bowel, bladder, femoral heads, and bone marrow [9–11, 22]. Our analysis confirms the superiority of proton therapy in sparing low integral dose to these critical OARs in cervical cancer patients (Figure 3A through 3C). There have also been randomized trials that have confirmed the benefit of modern radiation techniques decreasing treatment-related toxicities in women with gynecologic malignancies [15, 23], a benefit that may be further improved upon with IMPT.

One of the problems often encountered with treating pelvic malignancies using pencil beam scanning technology (or with the use of VMAT techniques) are the anatomic changes that can affect the dose distribution (ie, variations of bladder and bowel filling) to the target or OARs. It is important to note that patients with ovarian transposition are typically treated with VMAT to maximize ovarian sparing, and these uncertainties in position are common to both IMPT and VMAT techniques. Consensus guidelines [24] are available to account for such motion uncertainties, which were also followed for the IMPT planned patients. More specifically for IMPT, as an additional measure to assess anatomic changes during the course of treatment, quality assurance scans are performed. If any anatomic changes should occur, nominal dose distributions are re-planned on the quality assurance CT scan and compared with the initial CT simulation dose metrics to ensure that plan parameters remained constant throughout treatment [25]. Adaptive planning may ensue based on the physician discretion. Another limitation of our present study is not accounting for the dose contribution given from brachytherapy procedures, which remain crucial for cure in women with advanced cervical cancer [26]. Given the rapid dose fall off seen in brachytherapy procedures, the impact of brachytherapy on target and normal tissue dose distribution is likely minimal compared to photon therapy.
procedures for cervical cancer and use of modern image-guidance techniques to further optimize dose distribution [27], the additional radiation exposure is most likely minimal; however, it will be incorporated into future studies.

Furthermore, we do recognize that the greatest likelihood in achieving ovarian endocrine preservation in women who require WPRT for cervical cancer is a combination of ovarian transposition and modern radiation techniques. Indeed, in women who undergo ovarian transposition and receive WPRT (with or without brachytherapy), the rate of preserved ovarian function is only 65% [8]. This rate can be explained in part by the transposed ovary falling within the WPRT fields or strain on the blood flow to the ovary and thus can be potentially improved upon with advanced radiation methods using either proton therapy or VMAT. Moving forward, we would incorporate both patient populations (with or without oophoropexy) in prospective clinical trials.

Conclusion

In this feasibility study, we were able to consistently meet our dosimetric objectives in premenopausal women requiring WPRT to a prioritized ovary and clinical targets with IMPT, with improved integral dose to other OARs compared with VMAT. This study supports the notion that advances in radiation planning for women with cervical cancer may mitigate chronic side effects these women experience after definitive therapy. This study also supports future work focused on improving long-term toxicities in women with cervical cancer.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of Interest: The authors have no relevant conflicts of interest to disclose.

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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