Proton Therapy for Vaginal Reirradiation

Yun Rose Li, MD, PhD[1,2]; Maura Kirk, MS[2]; and Lilie Lin, MD[2]

[1]Medical Scientist Training Program, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
[2]Department of Radiation Oncology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Abstract

Primary or recurrent gynecologic cancers in operable patients with a history of prior pelvic radiation are typically treated with surgery based on the risk of late toxicities historically associated with reirradiation. A number of studies have demonstrated that, compared with conventional radiation therapy (RT) using photons, proton therapy (PT) offers dosimetric advantages for patients with gynecologic cancers by reducing radiation dose to healthy tissues. Thereby, we expect that, in appropriately selected cases, PT may reduce long-term treatment-related morbidities without compromising treatment efficacy. Herein, we describe the treatment planning, technique, and long-term follow-up of a patient who was treated with PT for a primary vaginal carcinoma nearly 30 years after a prior course of pelvic RT. Using this case, we illustrate the utility and advantages of PT in the treatment of cancers that occur at less favorable sites, adjacent to normal structures with low radiation tolerance, or in paients with a history of prior irradiation. Additionally, we provide a brief discussion and review of literature of prior case series of pelvic reirradiation, illustrating the value of identifying treatment approaches that can reduce treatment-related morbidities, particularly late treatment toxicities.

Corresponding author:
Lilie Lin
Department of Radiation Oncology
Perelman School of Medicine
University of Pennsylvania
3400 Civic Center Blvd,
PCAM/TRC 4West
Philadelphia, PA 19104 USA
Phone: +1 (215) 662-6515
Fax: +1 (215) 349-5445
Lilie.Lin2@uphs.upenn.edu

Introduction

Primary or recurrent gynecologic cancers in operable patients with a history of prior pelvic radiation are typically treated with surgery based on the risk of late toxicities historically associated with reirradiation [1, 2]. Recent studies, however, have demonstrated that proton therapy (PT) offers dosimetric advantages compared with conventional radiation therapy (RT) using photons for patients with gynecologic cancers [3]. By reducing the radiation dose to healthy tissues, protons may reduce long-term treatment-related morbidities without compromising efficacy. Consequently, protons may have utility in treating cancers that occur at less favorable sites, adjacent to normal structures with low radiation tolerance, or in this case, in a patient with a history of prior pelvic irradiation. Here, we describe the treatment planning, technique, and long-term follow-up of a patient who was treated with PT for a primary vaginal carcinoma nearly 30 years after a prior course of pelvic RT.

Case Presentation

The patient was a 58-year-old G3P3003 woman with a distant history of stage IIB squamous cell carcinoma of the cervix treated with radiotherapy alone 27 years ago. The patient signed an informed consent form for enrollment on an institutional review board approved study for proton radiation therapy. She presented with a 6-month history of painless vaginal bleeding and a 25-lb unintentional weight loss. Pelvic exam revealed a large, friable $5 \times 8 \times 10$ cm

Figure 1. Fluorodeoxyglucose-positron emission tomography/computed tomography. Intensely fluorodeoxyglucose-avid soft tissue mass in the upper vagina.
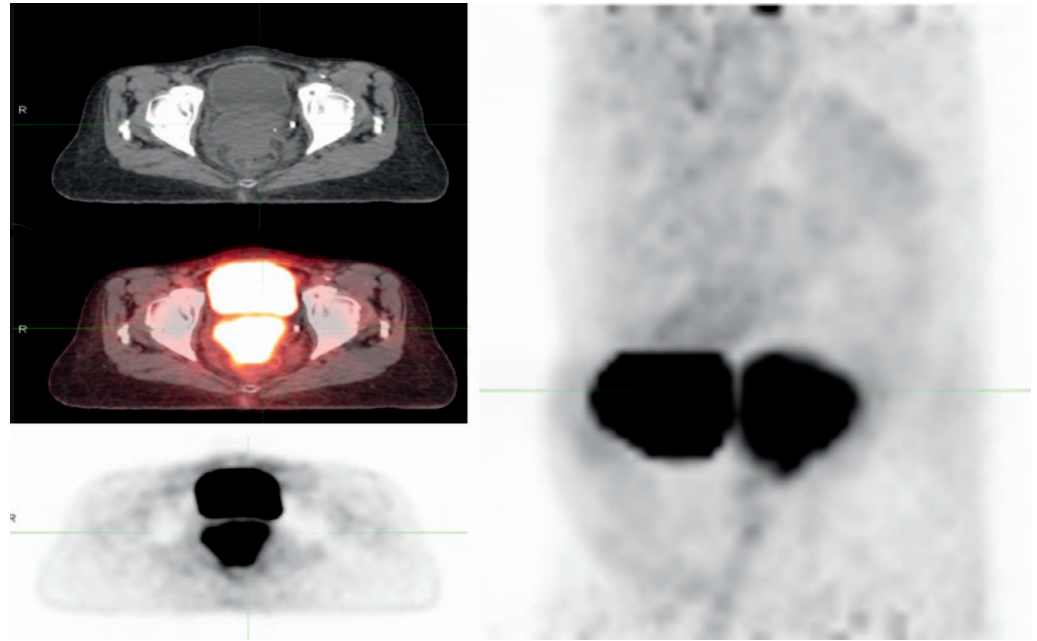
tumor vaginal mass arising from the posterior and lateral vaginal walls (2 to 6 o'clock position) and extending to the superior edge of the levators and distally to lower third of the vagina, 3 cm from the introitus. There was no parametrial extension.

Although the rectum was not adherent to the tumor, it appeared to be compressed by the tumor such that a wide excision would result in compromise of rectal function. The mass was hypermetabolic and measured $4.3 \times 5.1 \times 3.8$ cm on fluorodeoxyglucose-positron emission tomography–computed tomography without evidence of distant metastases (**Figure 1**). Biopsy confirmed the diagnosis of poorly differentiated invasive squamous cell carcinoma. Pelvic magnetic resonance imaging demonstrated a tumor extending to the levators but no evidence of extension into the pelvic parametria (**Figure 2A**). Although the rectum appeared to be compressed, a barium enema study found no evidence of rectal narrowing or mass effect on the rectum to suggest invasion by tumor.

Prior Radiation History

She received whole-pelvis RT using 4-field technique for cervical carcinoma to 39.6 Gy in 1.8 Gy fractions and a total parametrial boost of 16 Gy initially for her primary cervical carcinoma. In addition, she underwent 1 low-dose-rate intracavitary brachytherapy course via tandem and ovoid insertion to a total of 40 Gy prescribed to point A. Cumulatively, the total doses to point A were 79.5 and 80.2 Gy on the left and right sides, respectively, and the total doses to point B were 65 and 59.6 Gy, also on the left and right sides, respectively. The total International Commission on Radiation Units & Measurements doses to the bladder and rectum were 56.2 and 48.0 Gy, respectively.

Treatment Course

After the diagnosis of primary vaginal carcinoma was confirmed, the patient was strongly advised to undergo pelvic exenteration given her prior course of pelvic radiotherapy. As she refused further surgery, the patient was offered concurrent chemoradiotherapy (CRT) with limited-field RT (**Figure 3A**) and concurrent, weekly administered cisplatin 40 mg/m^2, as an alternative treatment. Given that the patient was previously treated with RT, we considered the value of using PT as opposed to intensity-modulated RT (**Figure 3B**) in an effort to spare radiation dose to the other organs at risk (OARs). The patient underwent standard positron emission tomography–computed tomography and magnetic resonance imaging simulation as previously described with endorectal balloon in place to reduce the risk of circumferential rectal irradiation [4]. Halfway through her PT, a replan was created due to the significantly reduced tumor volume, which substantially impacted the dose prescribed to OARs (**Figure 2B**).

After completing PT, the patient underwent high dose rate interstitial brachytherapy placement. The total dose to 2 cc (D2cc) for the complete course of radiotherapy, including external beam RT was 63.8 Gy (equivalent dose in 2 Gy fractions) and 58 Gy for rectum and bladder, respectively.

Figure 2. Magnetic resonance imaging (MRI) of the pelvis. (A) MRI confirms a 4.3 × 5.1 × 3.8 cm posterior vaginal wall mass without adenopathy. (B) Pretreatment sagittal T2 MRI of the pelvis (left) and midtreatment sagittal T2 MRI of the pelvis (right) showing dramatic reduction in size of the tumor. This demonstrates that treatment response should be monitored so that reimaging can be obtained as it can significantly reduce dose to organs at risk in some cases.
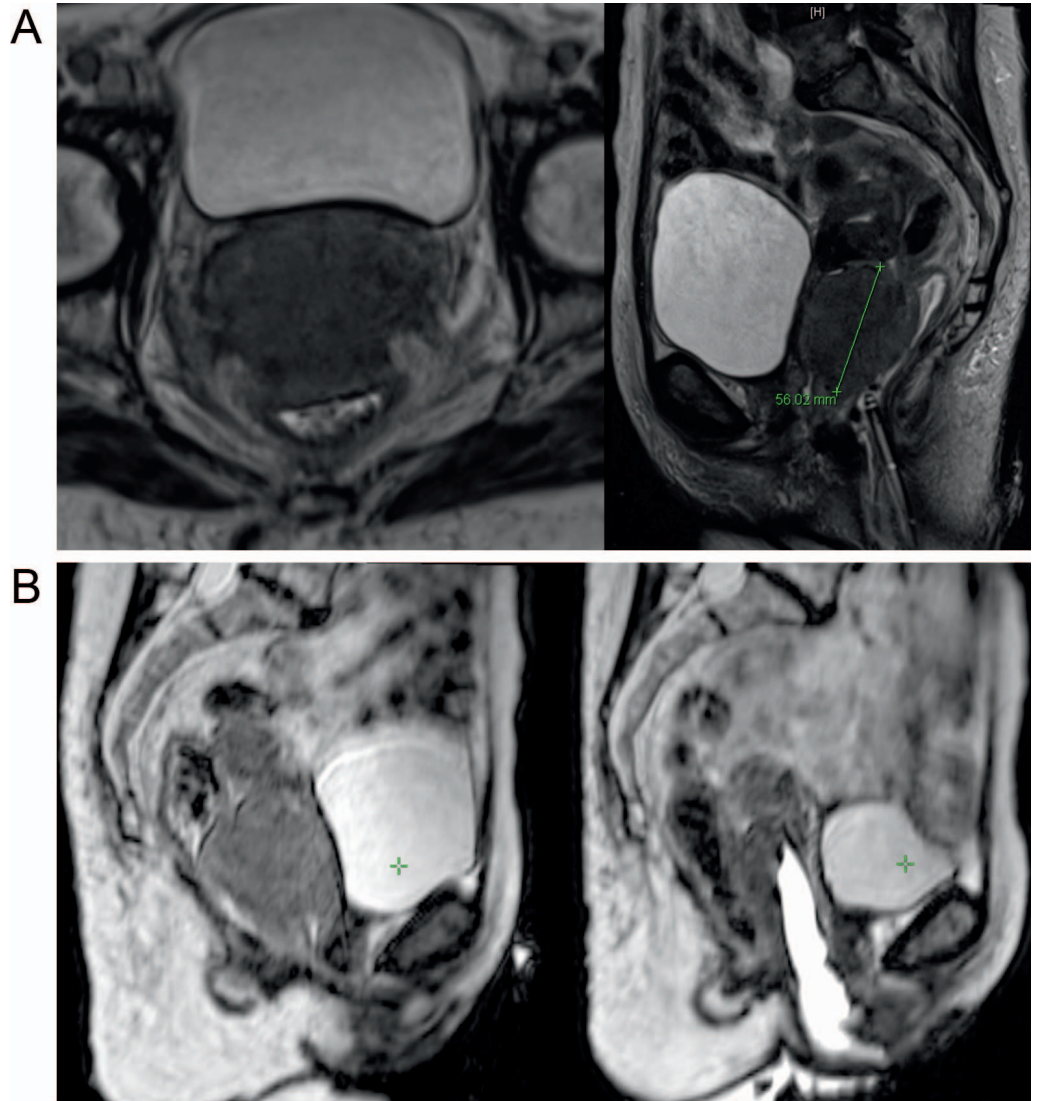

Outcome of Therapy

The patient completed the full course of treatment without experiencing any nonhematologic acute toxicities greater than grade 2 (Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer criteria) [5]. Over the course of nearly 5 years of follow-up, the most significant late toxicities she experienced were gastrointestinal, including grade 3 (per Common Terminology Criteria for Adverse Events [CTACE] 4.03) proctitis with mild to moderate stool incontinence, grade 3 rectal ulceration, and grade 3 bleeding mucosa requiring endoscopic treatment with argon plasma coagulation and hyperbaric oxygen therapy [6]. She also experienced grade 1 to 2 vaginal mucosal toxicity (telangiectasias, fibrosis, and vaginal shortening on exam), which did not interfere with the instrumental activities of daily living, physical examination or sexual activity (CTCAE, version 4.03). She has had no evidence of disease recurrence to date.

Discussion

In an aging population in which people are enjoying longer life expectancies, coupled with improved cancer diagnosis and survival rates, the need to treat patients who have a history of prior pelvic radiation has increased [7]. Women with cervical cancer have been shown to be at higher risk of secondary malignancies, including human papillomavirus–related malignancies as well as gastrointestinal cancers [8]. This risk has been shown to increase with time, even beyond 40 years after initial therapy. Some groups estimate a lifetime recurrence risk of 20% to 40% for "pelvic relapse" in patients with a history of a prior gastrointestinal/genitourinary cancer [9]. The rate may be higher in those previously treated with RT

Figure 3. Proton-photon comparison plans. (A) Dose color wash images showing the dose distribution from the proton therapy plan used for treatment (left) and the intensity-modulated photon plan generated for comparison (right) with the minimum color wash set to 10% of the prescription dose. (B) Dose-volume histogram comparing dose distributions when using an intensity-modulated radiation therapy (X) versus proton (P) plan. The ratios of the total structure volume versus relative radiation dose for the 3 major organs at risk (bladder, bowel, and rectum) are shown.
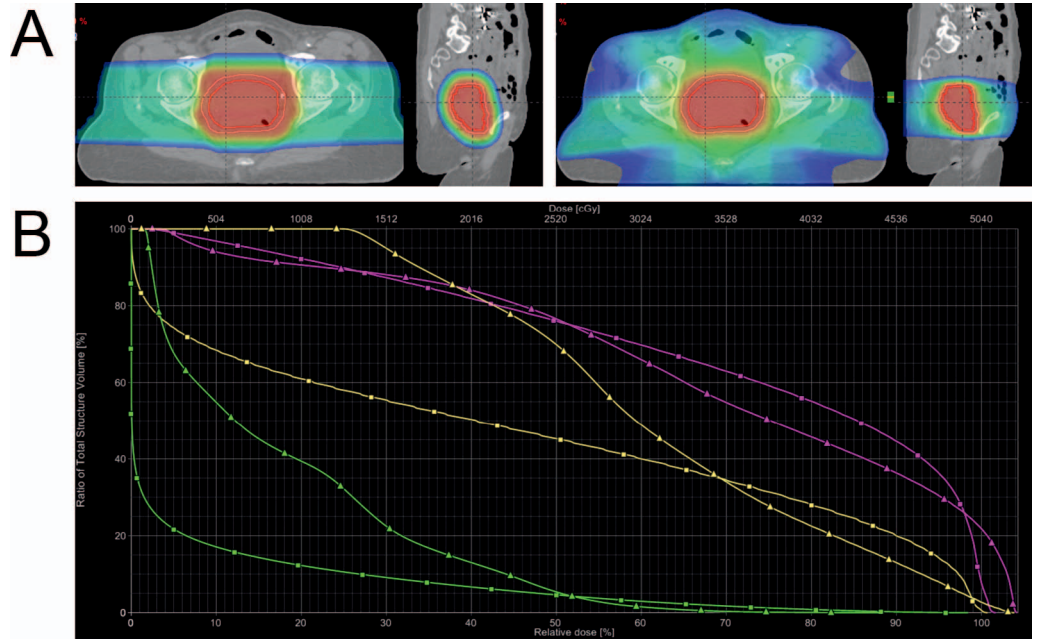
compared with those who were not. This is likely exacerbated by selection bias, as 80% of patients with pelvic relapse have had prior RT/CRT [10, 11], possibly because such patients had more advanced disease than those not receiving RT/CRT.

The standard of care for locally advanced, but resectable, pelvic recurrences and second primaries in a previously irradiated pelvis is surgical exenteration, which is the favored salvage approach in the approximately 10% of patients treated definitively [12]. However, exenterative surgery carries high rates of patient morbidity, including risks for chronic urinary tract infections, intestinal obstruction, and a 5% mortality rate related to surgical complications. Nonetheless, salvage surgery is often preferred over reirradiation, in part because reirradiation has been historically associated with a high risk of late colon or bladder toxicity [13, 14].

The clinical bias against reirradiating a previously treated pelvis appears consistent with the views of many practicing radiation oncologists illustrated by a 2010 survey showing that only 5% of Canadian radiation oncologists would treat a tumor occurring in a vaginal vault that has been previously irradiated [15]. As such, in most centers, RT or CRT is rarely utilized for definitive treatment, except in patients who are medically or surgically inoperable. In this case, the patient refused to undergo invasive surgery despite having resectable disease and multiple recommendations favoring pelvic exenteration.

This patient was an ideal candidate for proton treatment given that the clinical goals are aimed at minimizing radiation toxicity and total dose to the OARs while maintaining adequate tumor coverage. At the time of her treatment, only passive scattering PT was available at our institution. Pencil beam scanning, which is becoming more widely available, may provide superior conformality in a number of settings, for example [16], by reducing the proximal dose to the femoral heads and tissue lateral to the target by allowing for intensity modulated PT [17, 18]. Future improvements to proton beam delivery is anticipated with the implementation and availability of magnetic resonance imaging–guided approaches that incorporate magnetic modeling and Monte Carlo simulation [19].

As part of treatment planning, we also considered radiation dose to the OARs, namely the bladder and rectum. Unfortunately, very limited preclinical small animal studies or clinical data are available to guide evidence-based guidelines. The patient had previously received an estimated International Commission on Radiation Units & Measurements Bladder and Rectal point doses of 56.2 and 48 Gy, respectively, and during reirradiation was treated to a dose of 63.8 Gy to the rectum, which was within the D2cc max guidelines of both the American Brachytherapy Society (75 Gy) and Groupe Européen de Curiethérapie-European Society for Radiotherapy & Oncology (70 Gy) for primary radiotherapy [20, 21]. The bladder received a D2cc of 58 Gy, which was also within the D2cc guidelines as recommended by Groupe Européen de Curiethérapie-European Society for Radiotherapy & Oncology (90 Gy) [20]. While there are no specific recommendations in the context of reirradiation, we chose doses below 80% of the total dose, in keeping with those recommended by Jones et al [22].

In total, our patient has received a cumulative dose significantly higher than the estimated tolerance dose of the rectum when taking into account her prior radiotherapy. Consequently, we anticipated that there could be a greater than 50% risk of

Table 1. Patients receiving pelvic reirradiation for rectal cancers as reported in prior studies.[a]

Studies	No. of patients	C1 dose (Gy)	C2 dose (Gy)	C2 FX	Cumulative dose (Gy)	Cumulative NTD	Cumulative BED
Nieder et al, 2000 [25]	59	50.4 (range, 30–55)	40.8	BID	91.2	82.6	137.7
Russell et al, 1987 [2]	24	50.4 (range, 38–59.4)	39.6 (range, 30–45)	QD	90	86.4	143.9
Eifel et al, 1995 [27]	43	50.4 (range, 30–74)	34.8 (range, 15–49.2)	BID	85.8	77.6	129.2
Eifel et al, 1995 [27]	60	50.4 (range, 30–74)	34.8 (range, 15–49.2)	QD	85.8	81.8	136.3

Abbreviations: FX, fractionation; NTD, normalized total dose in 2 Gy fractions; BED, biological equivalent dose; BID, twice daily; C1, Course 1; C2, Course 2; QD, daily.
[a]Unless otherwise noted all doses are provided as medians.

grade 3 to 4 late toxicity, including radiation proctitis requiring surgical intervention and/or urgent hospitalization. The report from Jones et al [22] suggested that reirradiating at doses equivalent to ∼60% to 80% of the biologically effective dose normal tissue constraints appears to be well-tolerated based on small clinical studies of pelvic RT for secondary rectal malignancies (**Table 1**). As discussed later, we realized that this may be time dependent, as a number of groups have shown that time from prior radiation may inversely correlate with the degree of late tissue toxicity in patients requiring reirradiation [23, 24].

There is a relative paucity of data on the dose tolerance of healthy tissues in the setting of reirradiation, and most historical studies or case series have been insufficiently powered, making interpretation of negative findings difficult [25]. Thus, some radiation oncologists do not account for any effects of "late" tissue repair and therefore assume total cumulative dose constraints for the second course as the simple difference between the total acceptable dose to each organ and the dose previously delivered [26]. On the other hand, studies in animal models have suggested a 50% "dose-forgiveness," such that if a patient were to be reirradiated years after the first RT course, only half of the dose the patient initially received needs to be considered as the total dose previously delivered. However, the degree to which dose-forgiveness exists varies significantly in animal models compared with humans, and it appears to be a tissue-dependent phenomena related to the biology of normal tissue repair mechanisms.

Based on a review of existing literature from small-animal studies, Nieder et al [25] argue that tissues with little to no regenerating capacity, including the heart, bladder, and kidney, exhibit little capacity for late recovery. As a corollary, acutely responding tissues are the most likely to recover after a few months to years, and therefore, can better tolerate late retreatment. However, they caution that these preclinical studies were largely conducted before the availability of small-animal irradiators that can mimic modern-day modalities such as immune-modulated RT or stereotactic body RT. Moreover, they assert that to a large degree late tissue damage, including fibrosis, impaired blood perfusion and other local changes to normal tissues in such organs, continues for many years following treatment [25], making it more difficult to tease out primary versus retreatment effects. The heterogeneity in outcomes may also be a consequence of different priming doses and fractionation schemes across reports, as study parameters, particularly preclinical ones using animal models, vary significantly.

Russell et al [2] reported a series of 16 patients who underwent pelvic reirradiation, including whole-pelvis RT, brachytherapy, or combined modalities. They observed a 44% rate of achieving local control; however, 75% of those achieving tumor control developed grade 3 to 4 late complications. Fortunately, our patient has experienced only grade 3 or lower late gastrointestinal toxicities that have been manageable medically or by conservative endoscopic measure. She has not experienced any genitourinary toxicity beyond grades 1 to 2, consistent with other reports showing that the risk of rectal complications was on average greater than that of genitourinary complications [27]. Finally, it may also be important to consider the impact of concurrent, weekly chemotherapy in the overall toxicity experienced by the patients as prior studies of patients treated with reirradiation for rectal cancer have shown worse outcomes in terms of toxicity when concurrent CRT was administered [28].

Conclusion

In summary, while the management of a second primary vaginal cancer in a previously irradiated pelvis is clearly challenging, we present a case in which PT was successfully utilized as the definitive modality of treatment in the absence of surgical resection. Thus, we demonstrate that this is feasible and safe to consider in patients requiring reirradiation to the pelvis who are known to be inoperable or for whom surgical resection is not desired. In addition to the dosimetric advantages of PT in comparison to the use of immune-modulated RT, we also illustrated the value of close clinical follow-up during treatment in patients with bulky disease as midtreatment resimulation and replanning can significantly affect the total dose delivered to the

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OAR. The patient is thus far without evidence of disease recurrence and reports manageable toxicities that have been successfully treated by conservative measures. Larger series and longer-term follow-up studies are needed to assess this approach, however, and patients with cervical cancer should be followed long-term given the risk of developing second malignancies.

ADDITIONAL INFORMATION AND DECLARATIONS

References

1. Berek JS, Howe C, Lagasse LD, Hacker NF. Pelvic exenteration for recurrent gynecologic malignancy: survival and morbidity analysis of the 45-year experience at UCLA. *Gynecol Oncol*. 2005;99:153–9.

2. Russell AH, Koh WJ, Markette K, Russell KJ, Cain JM, Tamimi HK, Greer BE, Figge DC. Radical reirradiation for recurrent or second primary carcinoma of the female reproductive tract. *Gynecol Oncol*. 1987;27:226–32.

3. Lin LL, Kirk M, Scholey J, Taku N, Kiely JB, White B, Both S. Initial report of pencil beam scanning proton therapy for posthysterectomy patients with gynecologic cancer. *Int J Radiat Oncol Biol Phys*. 2016;95:181–9.

4. Rey F, Chang C, Mesina C, Dixit N, Kevin Teo BK, Lin LL. Dosimetric impact of interfraction catheter movement and organ motion on MRI/CT guided HDR interstitial brachytherapy for gynecologic cancer. *Radiother Oncol*. 2013;107:112–6.

5. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys*. 1995;31:1341–6.

6. Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. 2010. http://evs.nci.nih.gov/ftp1/CTCAE/About.html. Accessed October, 2, 2015.

7. Evans HS, Newnham A, Hodgson SV, Moller H. Second primary cancers after cervical intraepithelial neoplasia III and invasive cervical cancer in southeast England. *Gynecol Oncol*. 2003;90:131–6.

8. Chaturvedi AK, Engels EA, Gilbert ES, Chen BE, Storm H, Lynch CF, Hall P, Langmark F, Pukkala E, Kaijser M, Andersson M, Fossa SD, Joensuu H, Boice JD Jr, Kleinerman RA, Travis LB. Response: re: second cancers among 104760 survivors of cervical cancer: evaluation of long-term risk. *J Natl Cancer Inst*. 2008;100:600–1.

9. Andreu-Martinez FJ, Martinez-Mateu JM. Hypoxia and anaemia in patients with cancer of the uterine cervix. *Clin Transl Oncol*. 2005;7:323–31.

10. Thomas GM, Dembo AJ, Myhr T, Black B, Pringle JF, Rawlings G. Long-term results of concurrent radiation and chemotherapy for carcinoma of the cervix recurrent after surgery. *Int J Gynecol Cancer*. 1993;3:193–8.

11. Potter ME, Alvarez RD, Gay FL, Shingleton HM, Soong SJ, Hatch KD. Optimal therapy for pelvic recurrence after radical hysterectomy for early-stage cervical cancer. *Gynecol Oncol*. 1990;37:74–7.

12. Fuller AF Jr, Elliott N, Kosloff C, Hoskins WJ, Lewis JL Jr. Determinants of increased risk for recurrence in patients undergoing radical hysterectomy for stage IB and IIA carcinoma of the cervix. *Gynecol Oncol*. 1989;33:34–9.

13. Crowe PJ, Temple WJ, Lopez MJ, Ketcham AS. Pelvic exenteration for advanced pelvic malignancy. *Semin Surg Oncol*. 1999;17:152–60.

14. Anthopoulos AP, Manetta A, Larson JE, Podczaski ES, Bartholomew MJ, Mortel R. Pelvic exenteration: a morbidity and mortality analysis of a seven-year experience. *Gynecol Oncol*. 1989;35:219–23.

15. Joseph K, Tai P, Wu J, Barnes E, Levin W. Workshop report: a practical approach and general principles of re-irradiation for in-field cancer recurrence. *Clin Oncol (R Coll Radiol)*. 2010;22:885–9.

16. Giap BQ, Giap F, Einck JP, LePage R, Blasongame DM, Waldinger A, Dong L, Mascia A, Chang A, Rossi CJ, Giap H. A case study: proton therapy for male breast cancer with previous irradiation. *Int J Particle Ther*. 2016;2:579–83.

17. Moteabbed M, Yock T, Paganetti H. TU-A-108-10: pencil beam scanning vs. passive scattered proton therapy for pediatric thoracic/pelvic cancers. *Med Phys*. 2013;40:421.

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18. Hall EJ. Intensity-modulated radiation therapy, protons, and the risk of second cancers. *Int J Radiat Oncol Biol Phys*. 2006;65:1–7.

19. Oborn BM, Dowdell S, Metcalfe PE, Crozier S, Mohan R, Keall PJ. Proton beam deflection in MRI fields: implications for MRI-guided proton therapy. *Med Phys*. 2015;42:2113–24.

20. Potter R, Haie-Meder C, Van Limbergen E, Barillot I, De Brabandere M, Dimopoulos J, Dumas I, Erickson B, Lang S, Nulens A, Petrow P, Rownd J, Kirisits C, Group GEW. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. *Radiother Oncol*. 2006;78: 67–77.

21. Viswanathan AN, Beriwal S, De Los Santos JF, Demanes DJ, Gaffney D, Hansen J, Jones E, Kirisits C, Thomadsen B, Erickson B, American Brachytherapy Society. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part II: high-dose-rate brachytherapy. *Brachytherapy*. 2012;11:47–52.

22. Jones B, Blake PR. Retreatment of cancer after radical radiotherapy. *Br J Radiol*. 1999;72:1037–9.

23. Das P, Delclos ME, Skibber JM, Rodriguez-Bigas MA, Feig BW, Chang GJ, Eng C, Bedi M, Krishnan S, Crane CH. Hyperfractionated accelerated radiotherapy for rectal cancer in patients with prior pelvic irradiation. *Int J Radiat Oncol Biol Phys*. 2010;77:60–5.

24. Mohiuddin M, Marks G, Marks J. Long-term results of reirradiation for patients with recurrent rectal carcinoma. *Cancer*. 2002;95:1144–50.

25. Nieder C, Milas L, Ang KK. Tissue tolerance to reirradiation. *Semin Radiat Oncol*. 2000;10:200–9.

26. Eisbruch A, Dawson L. Re-irradiation of head and neck tumors. Benefits and toxicities. *Hematol Oncol Clin North Am*. 1999;13:825–36.

27. Eifel PJ, Levenback C, Wharton JT, Oswald MJ. Time course and incidence of late complications in patients treated with radiation therapy for FIGO stage IB carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys*. 1995;32:1289–300.

28. Berman AT, Both S, Sharkoski T, Goldrath K, Tochner Z, Apisarnthanarax S, Metz JM, Plastaras JP. Proton reirradiation of recurrent rectal cancer: dosimetric comparison, toxicities, and preliminary outcomes. *Int J Particle Ther*. 2014;1:2–13.

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