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Whole Pelvic Intensity-modulated Radiotherapy for Gynecological Malignancies: A Review of the Literature

Rockne Hymel¹, Guy C. Jones, M.D.², and Charles B. Simone II, M.D.³

Rockne Hymel: rhyme1@lsuhsc.edu; Guy C. Jones: guy.jones@nih.gov; Charles B. Simone: charles.simone@uphs.upenn.edu

¹Louisiana State University Health Sciences Center, School of Medicine, 1901 Perdido Street, New Orleans, LA 70112

²Radiation Oncology Branch, National Cancer Institute, National Institutes of Health, 9000 Rockville Pike, Bethesda, MD 20892

³Department of Radiation Oncology, University of Pennsylvania, 3400 Civic Center Blvd, Philadelphia, PA 19104

Abstract

Radiation therapy has long played a major role in the treatment of gynecological malignancies. There is increasing interest in the utility of intensity-modulated radiotherapy (IMRT) and its application to treat gynecological malignancies. Herein, we review the state-of-the-art use of IMRT for gynecological malignancies and report how it is being used alone as well as in combination with chemotherapy in both the adjuvant and definitive settings. Based on dosimetric and clinical evidence, IMRT can reduce gastrointestinal, genitourinary, and hematological toxicities compared with 3D conformal radiotherapy for gynecologic malignancies. We discuss how these attributes of IMRT may lead to improvements in disease outcomes by allowing for dose escalation of radiation therapy, intensification of chemotherapy, and limiting toxicity-related treatment breaks. Currently accruing trials investigating pelvic IMRT for cervical and endometrial cancers are discussed.

Keywords

IMRT; Radiation Therapy; Endometrial; Cervical; Gynecologic

Corresponding Author: Guy C. Jones, M.D., Center for Cancer Research, National Cancer Institute, Radiation Oncology Branch, NIH, 10 Center Drive, MSC 1682, Bldg 10/CRC/Room B2-3561, Bethesda, MD 20892, Phone: (301) 496-5457, Fax: (301) 480-5439, guy.jones@nih.gov.

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Authors' contributions

RH: Collected sources and provided substantial writing contribution

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1. Background

Whole pelvic radiation therapy (WPRT) is commonly employed for multiple gynecologic malignancies in the neoadjuvant, adjuvant, and definitive settings. To treat involved and at-risk lymph nodes, multiple WPRT techniques have been developed, including 3D-conformal radiotherapy (3D-CRT) and more recently intensity-modulated radiotherapy (IMRT).

3D-CRT typically employs either two (AP/PA), three (PA and opposed laterals), or four (AP/PA and opposed laterals) photon fields. Such WPRT techniques, while effective in controlling disease, result in irradiation of large volumes of small bowel, rectum, bladder and femoral heads to the full prescribed treatment dose, usually 45–50.4Gy in 25–28 fractions. In the adjuvant setting, such as following hysterectomy for endometrial cancer, small bowel may fall into the vacated space in the true pelvis, increasing bowel volume irradiated. This can increase the risks of acute and late gastrointestinal (GI) complications, limiting the dose that can be delivered to paracervical and nodal tissues at highest risk for recurrence. As a result, genitourinary (GU) and GI toxicities are commonly experienced in patients receiving conventional WPRT after hysterectomy.[1,2]

1.1. Emergence of IMRT

IMRT has evolved as a technique that can treat tumor or areas at risk of recurrence and nodal metastasis, while sparing adjacent normal tissues from high-dose irradiation. IMRT is an advanced form of radiotherapy that allows a varying intensity of irradiation across the path of the treatment beam. Figure 1 demonstrates comparison WPRT plans using standard AP/PA, 4-field (AP/PA and opposed laterals), and IMRT techniques. As opposed to conventional treatment planning techniques that utilize a variety of configurations of beams, wedges, and beam weightings until a desirable treatment plan is achieved, IMRT employs inverse planning in which dose-volume constraints and/or dose limits are inputted and an automated process derives an optimal treatment plan.[3] By selecting constraints to prioritize tumor volume coverage and normal tissue sparing, IMRT produces a more conformal treatment with irradiation to a desired target volume while decreasing dose to normal pelvic tissues, including small bowel, bladder, rectum, and femoral heads (Figure 1). IMRT is widely utilized to achieve more conformal treatment of irregular treatment volumes, including the treatment of prostate, GI, and head and neck cancers.

The major potential advantage of IMRT in treating gynecological malignancies is the ability to shape a dose distribution that delivers a lower dose to intraperitoneal pelvic contents than surrounding pelvic lymph nodes, making it possible to reduce acute and late side effects of treatment. Dosimetrically, studies have shown that intensity-modulated whole pelvic radiation therapy (IM-WPRT) treatment plans provide highly conformal dose to areas at risk of recurrence, with considerable sparing of surrounding normal tissues[4,5], including bone marrow[6,7], bowel, kidney (with extended para-aortic treatment), spinal cord[8], rectum, and bladder[9].

2. Dosimetric Studies

Early dosimetric studies sought to demonstrate the advantages of IM-WPRT. One study reported by Heron et al in 2003 compared alternative plans for 10 patients with gynecologic malignancies who underwent CT-planning for adjuvant radiotherapy. 3D-CRT was set up using a four-field technique, compared with seven-field IMRT plans, and patients were treated to 45Gy in 25 fractions to the internal, external, and common iliac nodal groups and upper 4cm of the vagina. IMRT showed a reduced volume receiving >30Gy compared to 3D-CRT in the following organs: small bowel reduced by 52%, rectum by 66%, and bladder by 36%. This study showed IMRT can reduce normal tissue volume irradiated, which could lead to fewer acute and late side effects in these organs.[9]

A dosimetric study by Lujan et al presented the potential of reduced hematologic toxicity with bone marrow sparing IM-WPRT (BMS-IM-WPRT). For 10 patients with cervical or endometrial malignancies, three radiotherapy treatment plans to 45 Gy were compared: four-field WPRT plan, IM-WPRT plan, and BMS-IM-WPRT. Dose-volume histograms (DVHs) showed BMS-IM-WPRT reduced the volume of BM receiving >50% of the prescribed dose (60.0%) compared with IM-WPRT (75.7%, $p<0.003$) and four-field WPRT (87.4%, $p<0.001$), while still allowing for similar target coverage and normal organ sparing. BMS-IM-WPRT plans substantially reduced the volume of iliac crests irradiated to >20 Gy and allowed for more modest improvements in lumbar spine and sacrum doses. The authors of this study recommended focusing on iliac crests in consideration of BMS-IM-WPRT, especially as 50% of the total pelvic BM resides in the iliac crests. This study supports that BMS-IM-WPRT reduces BM volume irradiated while maintaining other improvements in critical structure doses achieved with non-BMS-IM-WPRT.[7] This approach was adopted in recent IMRT trials, such as Radiation Therapy Oncology Group (RTOG) 0529 that evaluated pelvic IMRT for anal cancer.[10] Taken together, BMS-IM-WPRT may allow for improved chemotherapy compliance and further optimization of the systemic and radiation modification effects of chemotherapy.[6]

3. Reports on Toxicity and Efficacy

Following dosimetric comparisons, clinical studies of IM-WPRT were pursued. Mundt et al compared 15 patients with gynecologic malignancies who received 45Gy IM-WPRT to a control group of 25 patients who received 45Gy conventional WPRT. The clinical target volume (CTV) consisted of the upper half of the vagina, parametrial tissues, uterus (if present), and regional lymph nodes (common, internal and external iliacs). Cervical cancer patients were also treated with intracavitary brachytherapy (ICB) to an additional 30–40 Gy to Point A, whereas endometrial cancer patients were treated with ICB to an additional 20–25 Gy to the vaginal surface. The authors report ICB was not a factor in acute toxicity because it was delivered after pelvic radiotherapy completion. Compared with patients who received conventional WPRT, IM-WPRT lowered the rate of grade 2 GI toxicities (53.4% vs. 96.0%, $p=0.001$) and lowered the frequency of using antidiarrheal medications (20.0% vs. 73.3%, $p=0.001$).[11]

In 2003, Mundt et al conducted another study on 36 patients with gynecological malignancies who had received IM-WPRT in order to minimize irradiation dose to small bowel and rectum. These patients were compared to 30 patients that had previously received conventional WPRT. IM-WPRT achieved lower rates of chronic GI toxicity at 11.1%, compared to 50.0% for conventional WPRT ($p=0.001$). Compared with patients who received conventional WPRT, patients who received IM-WPRT experienced fewer grade 1 (30% vs. 8.3%), 2 (16.7% vs. 2.8%), and 3 (3.3% vs. 0%) toxicities.[12]

Further evidence supporting IM-WPRT came from Beriwal et al, who reported on 47 patients with endometrial cancer who received adjuvant IM-WPRT to 45–50.4Gy and vaginal cuff brachytherapy (10Gy in two fractions). Eight patients also had expanded volumes to treat the paraaortic area. At a median follow-up of 20 months, there were no pelvic recurrences. Late toxicities were minimal and included grade 1 small bowel in 25%, grade 1 rectal in 2%, and grade 1 bladder in 13%. The 3-year rate of grade 2 toxicity was 3.3%, with one patient developing grade 3 small bowel toxicity.[13]

More recently, Shih et al also demonstrated excellent outcomes and limited toxicity with IM-WPRT. In that study, 46 patients with high risk endometrial cancer received adjuvant IMRT without brachytherapy to a median dose of 50.4Gy in 1.8Gy daily fractions after hysterectomy and bilateral salpingo-oophorectomy. PTV included internal, external, and distal common iliac vessels plus two consecutive 7mm expansions. Chemotherapy was given to 30 patients (65%) either concurrently ($n=23$, typically cisplatin) or sequentially ($n=7$, typically cisplatin and paclitaxel) with IMRT. At 5 years, the relapse rate was 9%, disease-free survival (DFS) was 88%, and overall survival (OS) was 97%. Grade 3 toxicities were limited to one patient with acute GI toxicity and one with chronic GI toxicity (both grade 3). Overall, 35 patients (76%) experienced some degree of hematological toxicity, with higher grades generally occurring in the concurrent chemoradiation group.[14]

Although these studies all showed promise for the potential of IM-WPRT in reducing WPRT toxicities, limitations inherent in comparisons to historical controls limited their impact. There also existed considerable variation in rates of grades 1–3 toxicities between these studies, which further limited conclusions that could be drawn.

3.1. Gastrointestinal Toxicity

Acute GI toxicities of WPRT typically involve varying degrees of loose or more frequent stools, diarrhea, cramping, and abdominal discomfort. Late toxicities may arise months to years after WPRT and most commonly include intermittent diarrhea, intolerance to certain foods, malabsorption of vitamins, lactose and bile acids, and more severe toxicities like proctitis, obstruction, and fistulas. Both the dose delivered and volume of normal tissue irradiated impact the likelihood of developing radiation-related GI toxicity.[15] Several studies on WP-IMRT have demonstrated its potential to lower rates of acute and chronic GI toxicities and reduce needs for antidiarrheal medications compared with conventional WPRT treatment.[4,11,12] Toxicities from conventional WPRT may require the need for an extended treatment break, which has been well established in cervical cancer to decrease local control and OS.[16]

A 2002 study by Mundt et al studied acute GI and GU toxicities of 40 patients with gynecologic malignancies who underwent IM-WPRT compared to toxicities in 35 patients treated with conventional WPRT. All patients received 45Gy in 25 fractions to the upper half of the vagina, parametria, uterus (if present), and regional lymph node regions (common, internal, and external iliacs). Twenty-three patients (58%) received cisplatin chemotherapy and 24 patients (60%) underwent ICB after IM-WPRT. IM-WPRT delivered a mean of 98.1% of the prescription dose to the PTV and improved sparing of normal tissues. No patient developed Grade 3 toxicity, and Grade 2 GI toxicity was reduced by 31% (60% vs. 91%, $p=0.002$) compared with conventional WPRT. Additionally, 75% receiving IM-WPRT required no or infrequent antidiarrheal medication compared to 34% with conventional WPRT ($p=0.001$).[4]

3.2. Hematologic Toxicity

Hematologic toxicity is another common complication of WPRT, especially in patients receiving concurrent chemotherapy. Approximately 40% of bone marrow (BM) reserve is in the pelvis, making sparing of pelvic bones particularly important. Studies have demonstrated lower rates of hematological toxicities, including higher WBC and absolute neutrophil counts (ANC), resulting in fewer chemotherapy treatment breaks with IM-WPRT.[6]

Brixey et al reported on 36 patients who received IM-WPRT for uterine and cervical malignancies compared to 88 patients who received conventional four-field WPRT. The CTV for all patients included the upper half of the vagina, parametria, uterus (if present), presacral region, and regional lymph nodes (common, internal, and external iliac). Patients were treated to 45Gy in 25 fractions and underwent complete blood counts before and weekly during RT. DVHs showed significant reductions of pelvic bone marrow irradiated with IM-WPRT. Despite this, rates of grade 2 toxicities for WBC, ANC, and Hgb were similar between patients receiving IM-WPRT and four-field WPRT (all $p>0.05$) without chemotherapy. With the addition of chemotherapy, however, patients receiving conventional WPRT experienced higher rates of grade 2 WBC toxicity (60.0% vs. 31.2%, $p=0.08$), and lower WBC (2.8 vs 3.6microg/dL, $p=0.05$) and ANC (1874 vs 2669, $p=0.04$) counts compared to patients receiving IM-WPRT. IM-WPRT also achieved a 27.5% reduction in patients requiring holding of scheduled chemotherapy doses.

4. Dose Escalation

With greater sparing of normal tissues, it has become feasible to allow higher doses to be delivered to target volumes with IM-WPRT compared with standard WPRT. Dose escalation techniques have been shown to be feasible and improve outcomes in diseases like prostate cancer in the IMRT era.[17–20]

Para-aortic lymph node (PALN) metastases is the most important prognostic factor in locally advanced cervical cancer (LACC), but increasing dose to PALNs has the potential for increased bowel doses and worsening toxicities. A 2004 study by Ahmed et al examined IMRT dose escalation for PALN metastases by comparing WPRT using AP/PA, four-field, and IMRT techniques in 5 patients with LACC with PALN metastases. The dose to grossly positive PALNs was escalated from 45Gy to 60Gy in 2.4Gy daily fractions with IMRT.

IMRT to PALN metastasis reduced bone marrow and spinal cord exposure compared to the other two techniques. Compared to AP/PA, PALN-IMRT reduced the volume of bone marrow receiving >40Gy from a median of 98.0% to 21.3% ($p=0.0335$). With lower bone marrow dose that can reduce hematologic toxicities, IMRT may allow for less interruptions and higher doses of chemotherapy and decreased toxicity compared with conventional WPRT.[8]

5. Randomized Evidence

A recently published clinical trial from the All India Institute of Medical Sciences provides perhaps the best evidence of benefits of IM-WPRT. Ghandi et al reported on 44 patients randomly assigned to receive conventional WPRT vs. IMRT (50.4Gy in 28 fractions with concurrent cisplatin) for FIGO IIB-IIIB cervical squamous cell carcinoma. All patients received an ICB boost. Conventional WPRT plans delivered similar target coverage but comparatively higher doses to organs at risk compared with the WP-IMRT plans.

At a median follow-up of 27 months, disease-free survival and OS were not different between the groups, however WP-IMRT patients experienced fewer acute grade 2 and 3 GI toxicities compared with conventional WPRT patients (31.8% vs. 63.6%, $p=0.034$ and 4.5% vs. 27.3%, $p=0.047$, respectively). IM-WPRT also reduced chronic GI toxicities (13.6% vs. 50%, $p=0.011$). Rates of hematologic toxicities, however, were not significantly different between treatment arms.[21]

6. Feasibility of Inter-institutional Adoption of IM-WPRT

Recently, a phase II study assessed the feasibility of delivering reproducible WP-IMRT across multiple institutions. Among 58 patients accrued from 25 institutions, 43 eligible patients with endometrial adenocarcinoma were treated with IM-WPRT alone to 50.4Gy in 1.8Gy daily fractions to a vaginal-parametrial CTV and nodal CTV that included common, internal and external iliac and obturator nodes. Twelve patients (28%) developed grade 2 short-term bowel toxicity. Doses to critical normal structures exceeded protocol criteria in the following frequency: bladder 67%, rectum 76%, bowel 17% and femoral heads 33%. Contouring vaginal and nodal CTVs and delineating a specific bowel volume required a significant learning curve. With a detailed protocol, quality assurance, and monitored contouring, however, IM-WPRT was shown to be feasible across multiple institutions.[22]

7. Image-Guided Radiation Therapy

Perhaps the most important aspect of successful adoption of any new IMRT technique is the ability to accurately verify daily treatment setup positioning. Compared with standard 3DCRT approaches where a greater portion of the pelvis is treated, IMRT with its rapid dose fall-off, requires more precise setup verification to prevent a geographical miss.

Numerous studies have explored how pelvic organ motion and interfractional variation influences reproducibility of treatment delivery, including understanding the importance of patient positioning and effects of variations based on bladder and rectal filling.[23–27] Other studies have demonstrated changes in volume of bowel irradiated from one fraction to the

next, especially in postoperative cases.[28] For these reasons, various image-guided radiation therapy (IGRT) techniques have been developed and explored.

Chan et al explored the use of pelvic MRI weekly and prior to treatment in patient treated for cervical cancer. This study demonstrated that the GTV, cervix, and uterus may move substantially during the course of fractionated RT.[23] Follow-up studies using on-board imaging techniques such as cone-beam CT and Tomotherapy megavoltage CT with or without fiducial markers have also been explored, again demonstrating significant CTV movement with changes in bladder and rectal volume, consistent with the previous study using off-line MRI.[25,29,30] Now that these on-board imaging solutions are in widespread use, it is feasible that these IGRT techniques can be widely and optimally implemented.

Such IGRT studies are important not only for verifying daily treatment setup, but also for determining the most appropriate IMRT treatment planning margins to ensure optimal disease control while sparing normal tissues as much as feasible. These and other studies have explored this issue and proposed such margins based on a variety of methods. [24,31,32] An interesting adaptive IMRT strategy was recently proposed which uses a “margin of the day,” essentially selecting from a bank of radiation treatment plans with different CTV to PTV expansion margins to improve target coverage based on regular ultrasound bladder-volume measurements performed during treatment.[33] Although a novel approach, it may not be feasible in many clinics due to significant labor demands involved in producing several plans for each patient.

8. Future Directions

IM-WPRT has been the fastest growing indication for use of IMRT and has been among the top four most frequent treatment deliveries of IMRT. In a 2004 survey, 73.2% of 239 responding physicians used IMRT in 2004, compared to 32% in 2002. In this two-year period, IMRT use increased 62.7% among nonusers, and usage has continued to increase since. Physicians reported using IMRT to increase irradiation doses to target volumes while increasing sparing of normal tissues. The authors reported that “standardized guidelines are becoming necessary to ensure continued delivery of high-quality radiation therapy. Prospective controlled trials evaluating tumor control and treatment sequelae, with careful follow-up to monitor long-term risks and benefits, will be needed as more patients are treated with IMRT.”[34]

IMRT also requires an intricate understanding and recognition of anatomy and patterns of nodal failure for accurate target delineation, which had made widespread adoption of these techniques challenging. Recently, contouring atlases for WP-IMRT have been created and made available to the radiation oncology community through the RTOG.org website. Such atlases have been used successfully in other disease sites to improve IMRT reproducibility between institutions.

Additional information is needed to assess the candidacy of select patient populations for IMRT such as patients who are morbidly obese, those with significant bleeding, or other cases where the conservative nature of CTV/PTV planning design to avoid compromising pelvic control (determining if tight conformality of IMRT adversely affects oncologic

outcomes) is of concern. The case of intact cervix represents a particularly challenging scenario. While there is good data showing a dosimetric advantage of WP-IMRT in this scenario, the clinical data remains limited. Utero-cervical motion during treatment, dependent on bladder and rectal filling, necessitates generous treatment margins and probably dual simulation to obtain both full and empty bladder scans to assess the range of motion of the target organs and normal tissues under these extremes. Furthermore, tumor regression during chemo-radiotherapy can result in much greater doses to small bowel and bladder, thus WP-IMRT for intact cervix should only be used with IGRT and weekly pelvic examination during treatment may be recommended to assess response. Repeat simulation partway through treatment may also be required. In the end, the high dose areas are likely to be the high dose brachytherapy areas and benefits in terms of rectal and bladder toxicity are likely to be more limited for these patients. Until these issues are safely addressed, many believe the tight conformality of IMRT is ill-advised.

Several notable independent and cooperative group trials are currently attempting to answer many of the above questions and the safety and efficacy of WP-IMRT. Table 1 summarizes currently open trials accessing IMRT for gynecological malignancies.

9. Conclusions

WP-IMRT shows great promise in the treatment of gynecological malignancies by delivering therapeutic doses of irradiation with significantly greater sparing of normal tissues, including GI, GU, and bone marrow. Early studies show lower incidences of morbidities than for conventional 3D-CRT for patients treated for uterine and cervical cancer in the adjuvant setting and for uterine cancer in the definitive setting. For patients being treated definitively for cervical cancer, IM-WPRT should be used only with caution or preferably as part of a clinical trial. Current open trials will hopefully provide more evidence as to its feasibility, efficacy, and toxicity profile.

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Biographies

Dr. Rockne Hymel received his medical degree in 2014 from Louisiana State University Health Sciences Center, School of Medicine in New Orleans, Louisiana. He is currently performing his internship in Internal Medicine at Louisiana State University in anticipation of beginning his residency in Radiation Oncology at the Medical University of South Carolina in Charleston, South Carolina in July 2015.

Dr. Guy Jones is the Chief Resident in the Radiation Oncology Branch at the National Cancer Institute in Bethesda, MD with special research interests in CNS, thoracic, and gynecological malignancies. He graduated Summa cum Laude in Chemical Engineering from Washington State University in 2005 and completed his medical school studies at the New Jersey Medical School in 2010 where he was awarded the Alpha Omega Alpha Research Award. He completed a research fellowship with the Howard Hughes Medical Institute - National Institutes of Health Research Scholars Program. He has authored several peer-reviewed articles and has presented his work at national and international conferences.

Dr. Charles B. Simone, II is the Chief of Thoracic Oncology at the Hospital of the University of Pennsylvania. He completed his undergraduate training at the University of Pennsylvania and earned his medical degree from the Perelman School of Medicine at Penn. He completed residency training in radiation oncology at the National Cancer Institute (NCI), National Institutes of Health (NIH). Dr. Simone treats patients with lung cancer, malignant pleural mesothelioma, and other thoracic malignancies with photon and proton radiation therapy and photodynamic therapy (PDT). He is a NIH and Department of Defense funded investigator who performs clinical and translational research investigating the use of proton therapy and PDT as definitive therapy and as part of multi-modality therapy for non-small cell lung cancer, small cell lung cancer, and mesothelioma. Dr. Simone is the Co-Director of the Penn Mesothelioma and Pleural Program at Penn. He is appointed to the NRG Oncology (formerly Radiation Therapy Oncology Group [RTOG]) Lung Cancer Committee; Proton Collaborative Group (PCG) Lung Committee; International Thymic Malignancy Interest Group (ITMIG) Research Committee; ITMIG Thymic Carcinoma Workgroup; ASTRO Palliative Radiotherapy Working Group; American Society for Photobiology (ASP) Executive Council; ASP Education and Outreach Committee (committee Chair); and ASP Strategic Planning Committee. He is the Editor-in-Chief of *Annals of Palliative Medicine* and is on the Editorial Boards of *Journal of Thoracic Disease* and of *Frontiers in Oncology*.

Highlights

- IM-WPRT is the fastest growing indication for use of IMRT
- IM-WPRT for gyn cancers has the potential for better sparing of normal tissues
- Early studies show lower incidences of morbidities than for conventional 3D-CRT
- Ongoing trials seek to validate the use of IM-WPRT for gynecological malignancies

Figure 1.

Beam arrangement and treatment planning images. Representative treatment planning images for a 48 year old female with stage IB1 cervical carcinoma treated with concurrent cisplatin. Plans were generated using A) a two-field AP-PA technique, with images depicted in the B) axial, C) coronal, and D) sagittal planes. Plans were also generated using E) a four-field (AP-PA and opposed laterals) technique, with images depicted in the F) axial, G) coronal, and H) sagittal planes. Lastly, plans were generated using I) a seven-field IMRT technique, with images depicted in the J) axial, K) coronal, and L) sagittal planes. All plans delivered 45Gy in 1.8Gy daily fractions. The same slices from the same CT data set are depicted for Figures 1A, 1E, and 1I; Figures 1B, 1F, and 1J; Figures 1C, 1G, and 1K; and Figures 1D, 1H, and 1L. The aqua volume is the nodal PTV, and the magenta volume is the vaginal cuff PTV. Dose color wash coding: blue=50% to red=global max above 100%. This patient was also treated with a vaginal cuff boost using high dose rate brachytherapy.

Table 1

Open Trials Exploring Intensity-modulated Radiation Therapy for Gynecological Malignancies

Tumor Site	Clinical Trial ID	Name of Trial	Sponsor	Country	Year Opened	Patient Eligibility	Target Accrual	Randomized (Y/N)	Arms of Trial	RT Dose/Details	Primary Outcome
Endometrial	NCT01164150	Prospective Randomised Phase II Trial Evaluating Adjuvant Pelvic Radiotherapy Using Either IMRT or 3-Dimensional Planning for Endometrial Cancer	ICORG (All Ireland Cooperative Oncology Research Group)	Ireland	March 2010	Endometrial cancer s/p TAH with adjuvant radiotherapy indication(s)	154	Y	Pelvic 3DCRT + brachy versus pelvic IMRT + brachtherapy	45 Gy/1.8 Gy + 11/2 vaginal brachtherapy	Reduction in the incidence of grade 2 acute genitourinary and gastrointestinal toxicity
	NCT01641497	Phase III Study Comparing 3D Conformal Radiotherapy and Conformal Radiotherapy IMRT to Treat Endometrial Cancer	Centre Oscar Lambret	France	April 2012	Endometrial cancer s/p TAH with adjuvant radiotherapy indication(s)	60	Y	Pelvic 3DCRT versus pelvic IMRT	45 Gy/1.8 Gy	Change from baseline in acute toxicity
	NCT01672892	Standard Versus Intensity-Modulated Pelvic Radiation Therapy in Treating Patients With Endometrial or Cervical Cancer	RTOG (Radiation Therapy Oncology Group)	USA	Nov. 2012	Cervical or endometrial cancer s/p hysterectomy	281	Y	Pelvic 3DCRT versus pelvic IMRT	45–50.4 Gy/1.8 Gy	Acute gastrointestinal toxicity at 5 weeks from the start of pelvic radiotherapy
Cervical	NCT01793701	Intensity-modulated Radiotherapy for Locally Advanced Cervical Cancer (DEPICT)	Queen Mary University of London	Britain	July 2010	Cervical cancer FIGO stage IIB-IVA (any pelvic nodal status) and FIGO stage IB2 and IIA with pelvic nodal involvement	44	N	Chemoradiation (dose escalation) 27–30 fractions compared with the standard 28 fractions	Dose Levels: 1 50.2–54Gy 2 50.6–58Gy* 3 50.8–60Gy *current level	Rate of severe GI toxicity
	NCT01554397	Study With Intensity Modulated Radiation Therapy With Cisplatin to Treat Stage I–IVA Cervical Cancer	University of California, San Diego	Multi-national	Sept. 2011	Cervical cancer FIGO clinical stage I–IVA	425	N	45.0 Gy/1.8 Gy (intact) or 50.4 Gy/1.8 Gy (postoperative high-risk) IMRT with Cisplatin	45–50.4 Gy/1.8 Gy	Rate of acute grade 3 hematologic or clinically significant grade 2 GI toxicity compared to conventional RT with concurrent cisplatin
	NCT01554410	Intensity Modulated Radiation Therapy With Cisplatin and Gemcitabine to Treat Locally Advanced Cervical Carcinoma	University of California, San Diego	USA	August 2010	Cervical cancer stage IB2-IVA or stage I with biopsy-proven pelvic node metastases, positive surgical margins, or parametrial extension	18	N	45 Gy/25 fractions with Cisplatin and dose-escalating weekly gemcitabine	45 Gy/1.8 Gy	Establish the maximum tolerated dose of gemcitabine that can be safely administered in combination with Cisplatin