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Impact of postoperative intensity-modulated radiation therapy (IMRT) on the rate of bowel obstruction in gynecologic malignancy

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HIGHLIGHTS

- IMRT is associated with lower rate of bowel obstruction.
- Lower bowel obstruction rate was independent of other prognostic factors.
- Results of this study add further credence to the role of IMRT in gynecologic cancers.

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ABSTRACT

Objective. The purpose was to determine the potential impact of IMRT on the rate of bowel obstruction (BO), in patients with gynecologic malignancies undergoing postoperative pelvic RT.

Methods. We performed a retrospective review of all patients with endometrial or cervical cancer who received postoperative pelvic RT at our institution from 2000 to 2012. Patients who received definitive or palliative RT, or those with BO due to disease progression, were excluded. Standard two-sided statistical tests were used to evaluate for associated risk factors. Kaplan-Meier, Log rank and Cox proportional hazards regression analysis tests were performed for actuarial analysis.

Results. A total of 224 patients were identified, 120 (54%) received postoperative pelvic IMRT and 104 (46%) 3-dimentional (3-D) RT. Median follow-up time was 67 months. BO was grade 1 (asymptomatic) in 2/228 (0.9%), grade 2 (conservative management) in 4 (1.8%), and grade 3≥ in 4 (1.8%). Overall, the 5-year actuarial rate of BO was 4.8%. The 5-year rate of BO in the IMRT group was 0.9% compared to 9.3% for 3-D RT ($p = 0.006$). Patients with BMI ≥ 30 kg/m^2 were less likely to develop BO (2.6% vs. 8.3; $p = 0.03$). On multivariate analysis, only IMRT retained its significance as an independent predictor of less BO ($p = 0.022$).

Conclusions. The use of postoperative IMRT for cervical and endometrial cancer was associated with significant reduction in the rate of bowel obstruction. This difference maintained its statistical significance on multivariate analysis. Such finding if confirmed by others will help further solidify the benefit of IMRT in gynecologic cancers.

1. Introduction

Because the gastrointestinal epithelium has a high proliferative rate, it is especially susceptible to the effect of pelvic radiation therapy (RT). The majority of gastrointestinal toxicity related to pelvic RT is acute and can be effectively managed conservatively with bowel rest and/or pharmacologic agents. Bowel obstruction (BO), on the other hand, is a serious gastrointestinal complication that often requires hospitalization and may warrant surgical intervention. If left untreated, significant morbidity can result from BO such as bowel perforation, peritonitis, sepsis, bowel ischemia, or even death. The pathogenesis is related to direct radiation injury to mucosal stem cells within the crypts of Lieberkuhn or the result of microvascular damage. This vasculitis results initially in ischemia and inflammation, followed by fibrosis of the mucosa. [1] In turn this fibrosis results in decreased bowel motility. As such, the use of postoperative pelvic RT is associated with an increased risk of BO. This has

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been demonstrated in gynecologic malignancies, as well as other pelvic malignancies such as colorectal carcinoma. [2–4].

Compared with conventional 3-dimentional (3-D) RT, intensity modulated radiation therapy (IMRT) allows for delivery of highly conformal therapeutic radiation doses to oncologic targets while constraining the dose to healthy tissue. Several studies have demonstrated the dosimetric advantages of pelvic IMRT over conventional 3-D RT in gynecologic cancers as well as its clinical feasibility. [5–7] More importantly many investigators demonstrated that pelvic IMRT has a significant impact on reducing hematological toxicity when compared to 3-D RT [8,9], as well as better morbidity profiles for the genitourinary and gastrointestinal tracts. [10–12].

However, one area that has received little attention is the potential impact of postoperative pelvic IMRT on the risk of bowel obstruction. The primary objective of this study was to evaluate whether postoperative pelvic IMRT was associated with less incidence of bowel obstruction, given the improved side effect profile. The secondary objective of this study was to evaluate for other potential risk factors for bowel obstruction in patients with cervical or endometrial carcinoma who receive post-operative pelvic radiation therapy after hysterectomy.

2. Methods

After institutional Review Board (IRB) approval was obtained, an institutional database was queried to identify all patients with cervical or uterine cancer who received adjuvant pelvic radiation therapy (RT) after hysterectomy from 2000 to 2012 at Memorial Sloan Kettering Cancer Center. Only patients who received post-operative pelvic radiation were included; patients who received definitive or palliative RT were excluded. Patients with stage IV disease were also excluded.

Medical records including radiation, operative, pathology, chemotherapy, and radiology records were reviewed and clinical data were extracted. Specific clinical information was extracted, such as type of cancer (cervical vs endometrial), type of RT (conventional 3-D RT vs. IMRT), field of RT (pelvic vs. pelvic and para-aortic), body mass index (BMI), adjuvant chemotherapy, abdominal surgeries prior to hysterectomy, type of hysterectomy (simple vs. radical), approach of surgery (minimally-invasive vs. open), and extent of surgical staging (number of pelvic lymph nodes removed). Obesity was defined as a BMI ≥ 30 kg/m^2. The diagnosis of bowel obstruction was made radiographically. Patients who developed bowel obstructions in the setting of recurrent malignancy were excluded.

The technique of IMRT has been previously described. [6,7] In brief, contouring is performed in a manner similar to the Radiation Therapy Oncology Group (RTOG); for lymphatics, obturator, the internal, external, and common iliac vessels and presacral lymph nodes are contoured and two consecutive 7 mm expansions are applied to create a "pelvic lymph node planning target volume (PTV)" and "presacral PTV." The superior extent of the nodal PTV is the L4–L5 interspace; for a paraaortic field, the superior extent of the nodal PTV is the T12–L1 interspace. The inferior extent of the nodal PTV includes presacral lymph nodes to the level of S3 posteriorly and includes the external iliac nodes to the inguinal ligament. In terms of the "vaginal clinical target volume (CTV)," unlike the RTOG, where motion is accounted for by simulating with both full and empty bladder and incorporating elements of both scans to create ITV, our institution accounts for motion by using generous margins. The vaginal cuff contour (utilizing intravaginal contrast) is expanded initially by 2 cm to generate the "vaginal cuff CTV," and then an additional 1 cm axial expansion is applied to create the "vaginal cuff PTV." Weekly imaging was performed.

Clinical follow up consisted of vaginal exams every 3 months and Pap smear and CT chest/abdomen/pelvis every 6 months for the first 2 years. During years 3–4, patients received exams twice annually and Pap smear/imaging annually. Afterwards, exams and Pap smear were performed annually. All patient follow-up was performed at the primary institution. Grading of toxicity was based on the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, with the highest grade of any observed toxicity reported for each patient. Follow up and time to event was measured from the date of surgery to the last known visit or death. Standard two-sided statistical tests were used to evaluate for associated risk factors. Kaplan Meier method was used to calculate actuarial rates, with Log rank for comparison between variables. Cox proportional hazards regression analysis test was performed for multivariate analysis.

3. Results

A total of 224 patients were identified; all had received post-operative pelvic RT after hysterectomy for cervical or endometrial cancer. Clinical characteristics of the cohort are detailed in Table 1. The median age was 59 years (range, 23–85 years) and the median follow-up time was 67 months. The majority of patients had endometrial cancer (n = 152, 68%). The median body mass index (BMI) was 28 kg/m^2 (range, 18–58 kg/m^2). Ninety-five (42%) patients had undergone abdominal surgeries prior to hysterectomy. One hundred and twenty patients (54%) were treated with intensity modulated radiation treatment (IMRT) whereas 104 patients (46%) received conventional 3-D RT. The extent of the RT field was as follows; limited to pelvis in 185 patients (83%), extended to para-aortic region in 39 (17%). The median RT dose was 50.4 Gy. Adjuvant chemotherapy was given to 163 (73%) patients. For the 63 patients with cervical cancer it was given as concurrent cisplatin. For the 100 endometrial cancer patients, it was given concurrently in 78 patients and sequentially in 22.

Table 2 outlines the comparison between these two groups of patients. The IMRT and 3-D RT groups were comparable in terms of age, type of cancer, BMI, prior abdominal surgeries, and number of pelvic lymph nodes removed. The use of adjuvant chemotherapy was more prevalent in the IMRT group than 3-D RT (77% vs 67%, p = 0.09). Conversely, more patients underwent an open hysterectomy in the 3-D RT group than in the IMRT group (81% vs 47%, <0.0001). The median follow-up was 51 months in the IMRT group and 68 in the 3-D RT group. The median dose of radiation was 50.4 Gy in both groups.

In our cohort, 10 patients (4.5%) developed a bowel obstruction (BO) following post-operative pelvic RT. The median time to BO was 24 months (range: 7–65 months). BO was grade 1 (asymptomatic) in 2/224 (0.9%), grade 2 (conservative management) in 4 (1.8%), and grade 3 ≥ in 4 (1.8%). Overall, the 5-year actuarial rate of BO was 4.8% (95% CI 1.7–7.7). When considering grade ≥ 2 BO, the difference was still significant; 6.7% in the 3-D RT group vs. 0.8% in the IMRT group, p = 0.043.

Table 1
Patients and treatment characteristics (n = 224 patients).

		n	%
Age at diagnosis (years)	<60	123	55%
	≥60	101	45%
BMI (kg/m2)	<30	130	58%
	≥30	94	42%
Diagnosis	Endometrial	152	68%
	Cervical	72	32%
Prior abdominal surgeries	Yes	95	42%
	No	129	58%
Chemotherapy	Yes	163	73%
	No	61	27%
Type of hysterectomy	Open	141	63%
	Minimally invasive	83	37%
RT type	IMRT	120	54%
	3DRT	104	46%
Extent of RT	Pelvic	185	83%
	Extended field	39	17%
# of pelvic LN dissected	<10	61	27%
	≥10	163	73%