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Rectal bleeding after radiation therapy for endometrial cancer

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Abstract

Background & Purpose—The goals of this study were to determine the rate and risk factors of rectal bleeding (RB) after external beam radiotherapy and vaginal brachytherapy (EBRT+VB), and to compare this data to previously unreported RB rates from PORTEC-2 patients receiving EBRT or VB alone.

Materials & Methods—Retrospective chart review identified 212 endometrial cancer patients receiving adjuvant EBRT+VB between 2006–2013. Patient-reported RB data were also obtained from PORTEC-2 patients randomized to EBRT (n=166) or VB (n=182). The two populations were compared using an RB Scale of symptom severity.

Results—After a median 35 months, 17.9% of EBRT+VB patients (n=38) experienced any RB with 1.9% (n=4) having bleeding requiring intervention. Age ≥ 70 years was the only predictor of RB (OR 2.8; 95% CI 1.1–8.7; p=0.027). Rates of patient-reported RB after EBRT were similar with 15.0% (n=25) having any RB and 0.6% (n=1) having “very much” bleeding. On regression analysis, any EBRT (either EBRT alone or EBRT+VB) increased the risk of RB compared to those who received VB alone (OR 3.0; p=0.0028; 95% CI 1.4–6.7). The rates of more severe RB were low and did not significantly differ between treatments.

Conclusions—Significant RB is rare after radiation. The addition of VB to EBRT does not significantly alter bleeding rates.

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Conflict of Interest Statement

All authors declare that they have no conflicts of interest.

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Keywords

rectal bleeding; endometrial cancer; vaginal brachytherapy

INTRODUCTION

Endometrial cancer is the most commonly diagnosed gynecologic cancer in the United States and Europe [1,2]. Whereas low-risk disease, with well-differentiated endometrioid histology and superficial myometrial invasion is typically cured with surgery alone, much investigation has focused on the appropriate treatment for more advanced disease [3].

Three randomized controlled trials of intermediate-risk disease found that loco-regional recurrence (LRR) rates decreased from 9–14% without adjuvant treatment to 2–4% with adjuvant external beam radiotherapy (EBRT), though without significant improvement in overall survival. Notably, in all three trials, the majority of LRR events were vaginal [3–5]. This observation was the rationale behind the randomized PORTEC-2 trial that compared vaginal brachytherapy (VB) to EBRT for patients with high-intermediate risk features [6]. It has also been used as the rationale for combining VB and EBRT as a part of several randomized trials [7,8]. However, recent ASTRO endometrial-cancer guidelines concluded that vaginal brachytherapy may not always be warranted in patients also undergoing pelvic EBRT. The use of EBRT+VB was scored by the expert group as having low quality evidence and was given a weak recommendation, indicative of its controversial nature and the differing opinions on this topic [9]. No randomized controlled trials have yet investigated the efficacy of EBRT+VB compared to EBRT alone in more advanced disease. Interestingly, a SEER database analysis found that adding VB to EBRT improved overall survival in Stage IIIC disease with direct extension of the primary tumor [10]. In addition, *Aalders et. al.* and *Sorbe et. al.* found improved LRR rates with the addition of EBRT to VB, suggesting a possible rationale for more aggressive local treatment in high-risk patients [6–8].

With gastrointestinal toxicities being a well known complication of pelvic radiation, it is important to understand the potential long-term burden of more aggressive adjuvant therapy [11–14]. Randomized trials have established that VB is very well tolerated. When administered without EBRT in PORTEC-2, rectal bleeding was reported as a possible but rare complication [11,13]. In contrast, one retrospective series found that up to 5% of endometrial-cancer patients receiving VB after EBRT had rectal bleeding severe enough to require argon laser coagulation [14]. The goals of the current study are to investigate rectal-bleeding rates after radiation therapy for endometrial cancer and to establish possible predictors of bleeding. We examined rates of rectal bleeding in patients treated with combined EBRT+VB at a single institution as well as in patients who received either VB or EBRT in the PORTEC-2 study, using comprehensive, prospective patient-reported outcome data. Neither dataset has previously been analyzed for rectal bleeding.

MATERIALS AND METHODS

Retrospective chart review at the Dana-Farber/Brigham and Women's Cancer Center (DF/BWCC) was approved by the Institutional Review Board and identified 226 stage I-III endometrial cancer patients who received adjuvant EBRT+VB between 2006 and 2013 and had >1 year of follow-up. Ten patients were excluded for having diseases recurrence <3 months after radiation therapy and four were excluded for having adjuvant treatment with bevacizumab. This left 212 patients in the study. The medical record of each patient was examined to collect patient characteristics, disease characteristics, treatment parameters and outcomes. All patients in this population had a hysterectomy and bilateral oophorectomy with peritoneal washings. Depending on intraoperative findings, patients had further pelvic and/or para-aortic lymph-node dissection or sampling. EBRT was given to a median 45 Gy in 1.8-Gy fractions. VB was prescribed to the vaginal surface with a median 16 Gy delivered in 4 fractions. Patients with lymph-node involvement went on to have chemotherapy (cisplatin, carboplatin/taxol or gemcitabine/oxaliplatin). Patient follow-up included gynecologist, gynecologic oncologist or radiation oncologist visits every 3 months for 2 years, then every 6 months to 5 years, and annually thereafter. Chart review included evaluation of radiation plans to determine if any external beam boosts resulted in a boosted peri-rectal dose as well as assessment for use of antiplatelet agents and/or anticoagulation. All colonoscopy and sigmoidoscopy reports were also examined.

PORTEC-2 is a multicenter randomized trial designed to compare EBRT versus VB. Detailed patient selection and study design are described elsewhere [11]. In brief, patients were randomized to either EBRT or VB after surgery. EBRT was given to 46 Gy in 2-Gy fractions. Of patients receiving VB, 85% of patients received high dose rate treatment (21 Gy in 3 fractions) and 15% received low dose rate treatment (28–30 Gy in one session at 0.5–1 Gy/h). Rectal bleeding was assessed as a patient-reported outcome using EORTC PR-25, a cancer-specific quality-of-life questionnaire previously validated for prostate cancer with a focus on bowel and bladder symptoms [15]. Endometrial-cancer-specific quality-of-life questionnaires were not yet available when PORTEC-2 was active. A questionnaire was handed out at first consultation with a radiation oncologist (usually 3–4 weeks after surgery) and again 2–4 weeks after completing radiotherapy. Questionnaires were also sent to each patient's home 6, 12, 18, 24, 36, 48 and 60 months after randomization. In case of disease recurrence, quality of life assessment ceased and data was censored. The EORTC/RTOG grading system was used to record early and late radiation effects, including rectal bleeding as part of gastro-intestinal toxicity.

Reports and clinical interventions for rectal bleeding (RB) were evaluated and scored for both the DF/BWCC and PORTEC-2 data using the following scale: 0 was assigned for no documented evidence of bleeding on chart review or no patient-reported rectal bleeding; 1 was assigned for minimal bleeding documented on chart review with no further work-up or a patient report of "a little" bleeding; 2 was assigned for sufficient bleeding on chart review to have a subsequent colonoscopy without further intervention or a patient report of "quite a bit" of bleeding; 3 was assigned for bleeding on chart review which required argon laser coagulation and/or transfusion or a patient report of "very much" bleeding.

Statistical analyses were performed using JMP (SAS Institute, Cary, NC). For the single-institution series of patients receiving EBRT+VB, univariate and multivariate logistic regression were performed to estimate the odds ratio (OR) of association between each demographic, disease or treatment parameter and rectal bleeding. In the final regression analyses, parameters were considered significant at a two-sided p-value <0.05. To compare rates of rectal bleeding among groups treated with EBRT, VB and EBRT+VB, multivariate logistic regression was performed for the dependent variable of any rectal bleeding (RB 1–3) or higher-grade rectal bleeding (RB 2–3) using paired comparisons of radiation method (EBRT+VB versus EBRT, EBRT+VB versus VB, and EBRT versus VB). Because the available follow-up time was significantly different between the DF/BWCC and PORTEC-2 patient cohorts, each logistic regression comparing these two datasets included the covariate of time, defined as a continuous variable. In that analysis, parameters were considered significant at a two-sided p-value <0.0167 (0.05/3), corrected for the three treatment groups, EBRT, VB and EBRT+VB.

RESULTS

The demographic and treatment characteristics of the 212 endometrial-cancer patients who received EBRT+VB after hysterectomy at DF/BWCC and met inclusion criteria are described in Table 1. For comparison, the same characteristics of the patients in PORTEC-2 who answered the rectal-bleeding query on EORTC PR-25 at baseline and with at least one follow-up point are also described. Of the 427 patients treated in PORTEC-2, this criteria of survey completion was met by 77.6% (n=166) of the 214 patients who received EBRT, and by 85.4% (n=182) of the 213 patients receiving VB.

On average, the patients treated with EBRT+VB at DF/BWCC had more advanced disease than the patients in PORTEC-2. All patients who received EBRT-only or VB-only fell into one of three categories: (1) age >60 years with >50% myometrial invasion and grade 1–2 disease; (2) age >60 years with <50% myometrial invasion and grade 3 disease; or (3) any age, endocervical glandular involvement with <50% myometrial invasion and grade 1–2 disease. In contrast, EBRT+VB patients represent a broader spectrum of more advanced disease; 66% had FIGO 2009 Stage II–III disease, and thereby would have been excluded from PORTEC-2 (Supplementary Table 1). A total of 57% of EBRT+VB patients received chemotherapy while none did so in PORTEC-2 (Table 1).

The EBRT 4-field technique used in PORTEC-2 was similar to that used at DF/BWCC, with the main difference being 2-Gy fractions to 46 Gy for EBRT-only versus 1.8-Gy fractions to 45 Gy for EBRT+VB. None of the PORTEC-2 patients had an external beam boost whereas 8 women (3.8%) who received EBRT+VB had a cone-down boost to parametrial tissue or a suspicious lymph node that resulted in a higher rectal dose. The VB prescription for PORTEC-2 was 21 Gy in 3 fractions to a depth of 5 mm, and for DF/BWCC was 16 Gy in 4 fractions prescribed to the vaginal surface as a boost after 45 Gy EBRT.

As seen in Figure 1a, with a median follow-up of 35 months for EBRT+VB patients and 65 months for PORTEC-2 patients, >80% of patients in all three treatment groups had no symptoms or complaints of rectal bleeding. Overall, rectal bleeding of any severity was

experienced by 17.9% (n=38) of patients treated with EBRT+VB, 15.1% (n=25) of patients treated with EBRT alone, and 7.1% (n=13) of patients treated with VB alone. More significant rectal bleeding (RB scale 2 or 3) was reported by 4.7%, 2.4% and 1.6% of women in the EBRT+VB, EBRT-alone and VB-alone groups, respectively. Of note, no patient treated with VB-alone had a RB scale score of 3. The cumulative incidence of rectal bleeding is shown in Figure 1b. This Figure demonstrates that 95% of the total cases of rectal bleeding across the three treatment groups (72 of 76) were seen before 36 months. In addition, for all three groups, more severe rectal bleeding requiring intervention (RB Scale 3) was only seen between 6 months and 2 years after radiation.

It is notable in Table 1 that the median follow-up time from surgery differed significantly between patients treated with EBRT+VB and those treated with EBRT or VB alone. As a result, to compare rates of rectal bleeding between the DF/BWCC and PORTEC-2 patient cohorts, a multivariate logistic regression model to predict risk of rectal bleeding was created using follow-up time in months as a continuous variable and accounting for radiation treatment as various binary comparisons (EBRT+VB vs. EBRT, EBRT+VB vs. VB, EBRT +VB or EBRT vs. VB). Controlling for time, there was no significant difference in overall rectal bleeding (RB 1–3) between patients given EBRT+VB and patients treated with EBRT-alone. However, there was a significant difference in overall rectal bleeding (RB 1–3) in patients who received any EBRT (either EBRT alone or EBRT+VB) compared to those who received VB alone (OR 3.0; p=0.0028; 95% CI 1.4–6.7). Specifically, a significant difference was seen between EBRT alone and VB alone (OR 6.1; p=0.0002; 95% CI 2.27–18.22). The difference in overall rectal bleeding between the EBRT+VB and VB-alone cohorts showed a trend towards statistical significance (OR 2.2; p=0.035; 95% CI 1.06–4.93). There was no significant difference in higher-grade rectal bleeding (RB 2–3) rates among any of the three groups in the context of an overall small numbers of events.

While most EBRT+VB patients with RB Scale 2–3 had colonoscopy- or sigmoidoscopy-validated radiation-associated mucosal changes to account for the rectal bleeding, bleeding was reported by questionnaire for all PORTEC-2 patients. Colonoscopy or sigmoidoscopy to evaluate the rectal mucosa after radiation was performed on 17% (n=37) of patients treated with EBRT+VB. Notably, 43% (n=13) of patients with rectal bleeding had a colonoscopy or sigmoidoscopy at any time after radiation while only 13% (n=24) without rectal bleeding had similar recorded visualization of rectal mucosa.

The specific characteristics of the patients receiving EBRT+VB who developed higher-degree (RB 2–3) rectal bleeding are described in Table 2. Univariate logistic regression was performed to investigate possible factors, including disease recurrence, that influence the risk of any severity rectal bleeding after EBRT+VB. Of note, 76.4% of patients remained disease-free after treatment. Of those who recurred, only 1.4% initially recurred locally (including pelvic recurrence with or without vaginal involvement), and none had an isolated vaginal recurrence. Table 3 illustrates the odds ratio of rectal bleeding for each characteristic tested. Age < 70 years was the only variable tested which had a statistically significant association with rectal bleeding; 18% of patients in this younger age bracket developing rectal bleeding after radiation compared to 7% of those older than age 70 (OR 2.8; 95% CI 1.1–8.7; p=0.027). In the follow-up that was available, none of these patients developed

second primary cancers that could account for this bleeding. The use of antiplatelet agents (aspirin or clopidogrel) or anticoagulation (warfarin) was not significantly related to the incidence of rectal bleeding. Only 3 of 30 patients with rectal bleeding were on antiplatelet therapy and 1 was on anticoagulation. While 3 of 8 patients with rectal bleeding received a peri-rectal boost, this was too small a total number for rectal EQD2 to be associated with risk of rectal bleeding. An exploratory multivariable logistic regression model confirmed that younger age was the only significant variable associated with rectal bleeding; therefore multivariable regression was not included in the final analysis.

DISCUSSION

This study reports the rates of rectal bleeding for endometrial cancer patients treated with EBRT+VB, EBRT, and VB. This study goes on to assess potential prognostic factors for bleeding in the EBRT+VB treated population. EBRT+VB did not significantly increase RB rates when compared to EBRT, though the absolute rate of higher-degree rectal bleeding (RB scale 2–3) was 2.3% greater in the EBRT+VB group (4.7% vs. 2.4%). The absolute rate of RB Scale 3 bleeding requiring argon laser coagulation after EBRT+VB was 1.9%, which is less than the 5% previously published [14]. This may be due to the lower dose of 16 Gy in 4 Gy fractions used in this series while the previously published series administered brachytherapy at 15 Gy in 7.5 Gy fractions [14].

PORTEC-2 established VB as an excellent alternative to EBRT for high-intermediate risk, Stage I, endometrioid patients, in terms of efficacy for vaginal control and toxicity profile [3,11]. For “medium risk disease,” EBRT has been associated with a reduced pelvic recurrence rate (5.3% vs. 0.4%) when compared to VB alone [8]. Given the potential for mortality secondary to recurrence, EBRT remains indicated in high-risk patients to ensure pelvic control. While most randomized studies thus far have focused on patients with intermediate-risk disease, the addition of VB to EBRT could be particularly valuable in patients with a higher risk for vaginal recurrence. Such patients are likely to include those with clinical extension of disease to the cervix and involvement of the vagina. Parametrial or lymphatic spread are considered indications in some institutions but are not universally accepted indications for VB after EBRT.

Age 70 was the only patient-related predictor of increased risk of rectal bleeding, which is similar to the finding by *Kuku et. al.* that younger age was an independent predictor of post-pelvic radiation bowel toxicity in uterine-cancer patients [14]. The reasons for this are unclear. Younger age has been associated with a decreased risk of rectal bleeding in some prostate-cancer studies [16–19]. Whether younger patients with endometrial cancer have an increased risk of bleeding due to underlying biologic differences or possible genetic factors such as hereditary nonpolyposis colorectal cancer is unknown. While body-mass index, antiplatelet or anticoagulant use, and co-morbidities may play a role in propensity for post-radiation rectal bleeding, prior studies investigating risk factors for post-pelvic radiation rectal bleeding did not find a significant association with these variables [14,16]. This lack of association was also confirmed by our univariate analysis of these parameters in the EBRT+VB dataset.

While chemotherapy did not show a statistically significant association with rectal bleeding, the trend towards this effect suggests that the risk of rectal bleeding after EBRT+VB without chemotherapy may be less than what was observed overall. Of note, the rectal EQD2 was higher for EBRT+VB (median 56.6 Gy) than for either EBRT-alone (median 46 Gy) or VB-only (median 42 Gy). EBRT and VB would also be expected to differ in terms of the rectal volumes receiving radiation. However, despite these differences, the lack of association between rectal EQD2 and rectal bleeding as well as the small range of rectal EQD2 values across the various treatments suggest that these radiation parameters are less likely to explain the difference in outcome between the groups.

Limitations of this study include the use of different patient cohorts for comparison (ie- PORTEC-2 and DF/BWCC). The differences between these cohorts are particularly remarkable with regards to stage of disease and treatment strategies in the context of more advanced disease in the DF/BWCC population. In addition, the PORTEC-2 data was collected from prospective patient-reported outcomes while the DF/BWCC data was collected from retrospective chart review. Therefore, an RB scale was needed to compare these datasets, with inherent assumptions regarding the relative severity of RB. In addition, studies comparing patient reported outcomes with clinician-assessed toxicity suggest there is often some degree of underreporting with retrospective chart review that would effect RB rates in the EBRT+VB cohort [20,21].

It is also notable that follow-up time differed significantly between patients receiving EBRT +VB and patients receiving EBRT or VB alone; the median follow-up was 35 months in the DF/BWCC cohort and was 65 months in the PORTEC-2 cohort. However, as shown in Figure 1b, 95% of total rectal bleeding occurred before 36 months and more severe rectal bleeding (RB Scale 3) was not observed after 24 months, suggesting that this difference in follow-up time is unlikely to explain relative rectal bleeding rates. Further supporting this assessment is the fact that length of follow-up was included as a continuous variable in constructing our multivariate regression models to compare rectal bleeding rates between different treatments. In doing so, follow-up time was not found to be significantly associated with likelihood of bleeding (data not shown).

This study was unable to definitively evaluate the cause of rectal bleeding for patients who did not have direct visualization of the rectal mucosa by colonoscopy or sigmoidoscopy. Given the high prevalence of hemorrhoids or other radiation-independent etiologies of rectal bleeding in the general population, it may be reasonable to assume that a significant number of RB level 1 patients in all 3 treatment groups did not have radiation proctitis but rather had a radiation-independent cause of bleeding. However, patients with more severe bleeding requiring further investigation or treatment (RB 2–3) may be more likely to have radiation proctitis or other radiation-dependent causes of bleeding; therefore, comparison of more severe bleeding is likely to be of greatest interest and most accurately recorded. Since a secondary malignancy could be a possible cause of RB, the records of each patients with RB were specifically evaluated for this development. It was found that one VB patient developed a second cancer in the recto-sigmoid two years after indicating ‘a little bleeding,’ and was kept in this analysis.

Overall, while VB-alone has been established to be very well tolerated with minimal late gastrointestinal and genitourinary toxicities, there has been concern that adding VB to EBRT will amplify the toxicities of EBRT, such that any incremental improvement in disease control is negated by an untenable toxicity profile [14]. As might be expected, this study shows that EBRT significantly increases the risk of RB when compared to VB-alone. This study also found that the addition of VB (as 16 Gy in 4 Gy fractions) to EBRT resulted in an absolute 2.9% increase in RB but this change was not statistically significant. Overall, the risk of RB in patients treated with combined EBRT and low-dose VB may be countered by the benefits in terms of disease recurrence for patients with high-risk features. Therefore EBRT plus low-dose VB remains a treatment option to be considered for high-risk patients with an increased risk of vaginal recurrence, especially those with vaginal involvement, positive margins, or cervical stromal invasion.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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a.)

RB Scale	Criteria	EBRT alone (n=166)	VB alone (n=182)	EBRT+VB (n=212)
0	No bleeding	84.9% (141)	92.3% (169)	82.1% (174)
1	"A little" bleeding / no work-up or intervention	12.6% (21)	5.5% (10)	13.2% (28)
2	"Quite a bit" of bleeding / with work-up (e.g., colonoscopy)	1.8% (3)	1.6% (3)	2.8% (6)
3	"Very much" bleeding / requiring intervention (e.g., argon laser coagulation)	0.6% (1)	0% (0)	1.9% (4)

b.)

Figure 1. Rectal bleeding (RB) Scale Definition and Patient Distribution

(a) "RB Scale" defined and the relative frequency of patients developing RB reported from PORTEC-2 (EBRT-only and VB-only) and the single-institution series (EBRT+VB). (b) The cumulative incidence of new rectal bleeding for patients treated with each of three radiation modalities.

Table 1

Comparison of patient and treatment characteristics

	EBRT alone (n=166)	VB alone (n=182)	EBRT+VB (n=212)
Patient characteristics			
Median age, y (range)	69 (52–88)	69 (46–86)	64 (34–91)
Median BMI (range)	27.6 (17–45)	28.5 (20–51)	29.8 (17–63)
IBD, % (n)	1.2 (2)	1.1 (2)	0.5 (1)
Diabetes, % (n)	11.4 (19)	17 (31)	18.9 (40)
Hypertension, % (n)	37 (61)	34.8 (63)	51.9 (110)
Median follow-up from surgery, mos (range)	65 (18–106)		35 (12–84)
Treatment characteristics			
Adjuvant chemotherapy, % (n)	0	0	56.6 (119)
Median external beam radiation dose, Gy (range)	46 (40–48)	n/a	45 (41.4–64.8)
Boost (5.4–19.8 Gy) including peri-rectal area, % (n)	0	0	3.8 (8)
Median rectal EQD2, Gy (range)	46 (40–48)	42 (14–78)	56.6 (52–76)
Median vaginal brachytherapy dose, Gy (range)	n/a	21 (21–21)	16 (12–18)
Median time elapsed during radiation, days (range)	31 (25–39)	14 (14–14)	56 (38–103)

Key: y = years; BMI = body mass index; IBD = inflammatory bowel disease; % = percent; n = absolute number of patients; mos = months; Gy = Gray; EQD2 = 2-Gy equivalent dose.

Table 2

EBRT+VB patients with RB 2–3 rectal bleeding

Affected Patients			Patient Characteristics			Tumor Characteristics			Treatment Characteristics			Follow-up	
Patient ID	RB Scale	Age (yrs)	CCI	Anti-plt/coag	Stage	Histology	Grade	LVI	Chemo	EB dose, including boost (Gy)	Rectal EQD2	Follow-up time (mos)	Recurrence Site
1	3	72	0	N	IB	Endo	2	Y	N	45	57.3	23	N
2	3	55	2	N	II	Endo	2	Y	N	45	57.3	70	N
3	3	68	0	N	IIIC1	Endo	1	Y	Y	50.4	62.7	34	N
4	3	68	1	N	IIIC2	CC	3	Y	Y	55.8	57.5	33	LN
5	2	56	0	N	IA	PS	3	Y	Y	45	56.6	79	N
6	2	58	0	ASA	IB	Endo	1	N	N	45	56.6	35	N
7	2	79	0	ASA	IIIB	PS	3	Y	Y	50.4	60.2	25	N
8	2	60	0	N	IIIC1	Endo	1	Y	Y	45	56.6	33	N
9	2	77	1	N	IIIC1	Endo	3	N	Y	45	57.5	47	N
10	2	59	0	N	IIIC2	PS	3	N	N	45	56.6	47	N

Key: EBRT = external beam radiation therapy; VB = vaginal brachytherapy; RB = rectal bleeding; ID = identification number; yrs = years; CCI = Charlson Comorbidity Index; Antiplt/coag = antiplatelet or anticoagulation; LVI = lymphovascular invasion; Chemo = chemotherapy; EB = external beam; Gy = gray; EQD2 = 2-Gy equivalent dose; mos = months; N = no or none; Y = yes; ASA = aspirin; Endo = endometrioid; CC = clear cell; PS = papillary serous

Table 3

Odds ratio of univariate predictors of rectal bleeding

Patient Characteristics	UV OR (95% CI)	p-value
Age (< 70 yrs vs. ≥70 yrs)	2.8 (1.1–8.7)	0.027*
BMI (< 25 vs. ≥25)	1.5 (0.6–3.6)	0.35
Hypertension (+ vs. –)	1.75 (0.8–3.9)	0.16
Diabetes (+ vs. –)	1.2 (0.5–3.7)	0.74
Vascular disease (+ vs. –)	1.0 (0.3–4.4)	0.99
Antiplatelet use (+ vs. –)	2.1 (0.7–9.2)	0.2
Anticoagulant use (+ vs. –)	1.7 (0.3–31.7)	0.61
Disease characteristics		
Stage (I/II vs. III)	0.6 (0.3–1.4)	0.6
Histology (Endometrioid vs. Other)	0.6 (0.2–1.3)	0.2
Lymphovascular Invasion (+ vs. –)	0.6 (0.3–1.4)	0.3
Treatment characteristics		
Adjuvant chemotherapy (+ vs. –)	0.5 (0.2–1.1)	0.1
Carboplatin/Taxol	0.5 (0.2–1.1)	0.09
Oxaliplatin/Gemcitabine	0.9 (0.1–17.0)	0.9
Concurrent cisplatin	0.5 (0.1–3.9)	0.49
External beam (< 45 Gy vs. ≥45 Gy)	1.1 (0.4–3.6)	0.79
Peri-rectal boost (5.4–19.8 Gy)	3.9 (0.8–17.0)	0.09
Rectal EQD2 (<58 Gy vs. ≥58 Gy)	1.7 (0.6–7.5)	0.38
Outcomes		
Any disease recurrence	0.5 (0.1–1.3)	0.19
Recurrence in the pelvis	0.6 (0.03–3.2)	0.59

Key: UV = univariate; OR = odds ratio; yrs = years; BMI = body mass index; + = present; - = absent; Gy = Gray; EQD2 = 2-Gy equivalent dose

* p<0.05