Assessment of Risk of Late Rectal Bleeding for Patients with Prostate Cancer Started on Anticoagulation Before or After Radiation Treatment

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Abstract. *Aim: To evaluate the risk of late rectal bleeding and its association with the timing and type of anticoagulation use in patients receiving dose-escalated radiation therapy (RT) (≥7,560 cGy) for prostate cancer. Patients and Methods: Between 2003-2010, 465 patients were treated at our Institution with dose-escalated RT and included in this analysis. Patients were placed into the following categories: no anticoagulation use, aspirin during RT, clopidogrel/warfarin during RT, aspirin after completion of RT, clopidogrel/warfarin after completion of RT. Results: The overall bleeding rate was 7.5%. For those on aspirin during RT, the 4-year freedom from rectal bleeding (FFBS) rate was 91%, compared to 94.7% for patients who were never on anticoagulation (p=0.16). For those on warfarin/clopidogrel during RT the 4-year FFBS rate was 78.2%, compared to 94.7% in those never on anticoagulation (p<0.001). On multivariate analysis, use of warfarin/clopidogrel during radiation treatment were strongly associated with an increased risk of rectal bleeding (multivariate HR=4.84, 95% CI=1.84-12.68, p=0.001). However, initiation of anticoagulation after completion of radiation treatment did not significantly increase the risk of rectal bleeding (multivariate HR=0.78, 95% CI=0.21-2.91, p=0.71). Conclusion: The use of clopidogrel or warfarin during radiation is associated with significantly increased risk of rectal bleeding. However, initiation of these medications after completion of radiation does not appear to impact such risk.*

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Multiple large studies have shown that dose escalation results in improved outcomes for patients with localized prostate cancer (1-5), which have led to its adoption as a standard recommendation by the National Cancer Care Network (NCCN) (6). One recent report with 66 months' follow-up revealed that with the use of intensity-modulated radiation therapy (IMRT), the rate of gastrointestinal toxicity –namely bleeding, was approximately 5% (7). However, a recent meta-analysis revealed that while IMRT was associated with decreased gastrointestinal toxicity compared to three-dimensional conformal radiation therapy (3DCRT), there was an overall increase in late gastrointestinal toxicity with dose escalation (8).

Two recent retrospective studies reported an increased risk of rectal bleeding associated with anticoagulation use (9, 10). However, neither analyzed the risk by agent (aspirin compared to plavix/clopidogrel), nor was the timing closely analyzed to determine whether there is a difference between anticoagulation use concomitant with the radiation compared to afterwards. Therefore, in this retrospective study with long-term follow-up, we sought to analyze whether anticoagulation use is associated with an increased risk of late rectal bleeding and whether the timing plays a role in the bleeding risk.

Patients and Methods

After approval by our Institutional Review Board, we analyzed our database of 469 patients who received dose-escalated radiation therapy (minimum dose 7560 cGy) between 2003-2010 for localized prostate adenocarcinoma at our the Department of Veterans Affairs, NY Harbor Hospital, Brooklyn campus. A total of four patients were excluded because they had incomplete information regarding their medications that were being received outside of our healthcare system and were not properly documented. This left 465 patients to be included in the current study.

The patients' medications were recorded for every visit to the Radiation Oncology Department, as well as on numerous other

Table I. *Summary of anticoagulation use*.

Use of anticoagulation	Number (%)
None	181 (38.9%)
Aspirin during radiation treatment	137 (29.5%)
Asprin started after radiation completed	59 (12.7%)
Aspirin during radiation treatment, clopidogrel/warfarin started after radiation treatment	21 (4.5%)
Clopidogrel/warfarin during radiation treatment	42 (9%)
Clopidogrel/warfarin started after radiation completed	25 (5.4%)

inpatient and outpatient clinic notes. We separately recorded whether or not patients were on aspirin, clopidogrel, or warfarin, both at the onset of their radiation treatment, as well as during their follow-up visits throughout our medical system. The medical records of patients who moved out of the local area but maintained follow-up within our medical system were also analyzed.

The radiation techniques have been previously described (11). Briefly, the radiation techniques evolved over time from three-dimensional 3DCRT in 2003 to IMRT in 2007, to image-guided radiation therapy, consisting of daily megavoltage cone beam CT scans matched either to the bony anatomy or to gold fiducial markers in 2010. The radiation fields were typically limited to the true pelvis or prostate, and seminal vesicles for patients with NCCN low- or intermediate-risk disease. However, those with high-risk disease usually had their whole pelvis included in the initial field. Those receiving 3DCRT generally had a cone down after 4500 cGy that consisted of the prostate plus 1.2 cm all around. An additional cone down was designed at 7200 cGy that consisted of the prostate plus 0.6 cm all around. Until 2009, for the IMRT margins, the initial 4500 cGy consisted of the prostate plus 1 cm all around except 0.8 cm posteriorly, followed by a cone down of 0.8 cm all around and 0.5-6 cm posteriorly. The dose constraints for the rectum included 70 Gy <20%, 65 Gy <35% and 60 Gy <50% of the rectum. Starting in 2010 when image-guided radiation therapy was initiated, the posterior margins were changed to 5 mm and 4 mm respectively. In addition, the rectal dose constraints were tightened by 5% from the values noted above. All patients were treated at 180 cGy per fraction.

Generally, patients who received androgen deprivation (ADT) were treated neoadjuvantly for 1-2 months, followed by concurrent ADT with radiation, followed by further adjuvant ADT at the discretion of the treating physician. Most often, patients with intermediate-risk disease were treated for a total of six months, and patients with high-risk disease were treated for a total of two years.

Patients returned for follow-up appointments every 3-6 months for the first five years and then yearly. We reviewed both our clinical charts, as well as the inpatient and outpatient notes from all of the other departments within our medical system.

Toxicity was evaluated based on the medical documentation. Rectal bleeding was graded as follows. Grade 1 was self-limited rectal bleeding resolving without any intervention. Grade 2 was bleeding that required medications or bleeding that was intermittent/recurrent in nature. Grade 3 was bleeding that required an invasive intervention, which typically included argon plasma coagulation. Grade 4 was bleeding that required a transfusion or surgery. Grade 5 was bleeding that was associated with death. Gastroenterologists were typically very aggressive in evaluating rectal bleeding after radiation therapy and therefore most patients with intermittent bleeding were assessed *via* colonoscopy.

Table II. *Description of patient characteristics*.

NCCN Risk group	
Low	119 (25.6%)
Intermediate	203 (43.7%)
High	143 (30.8%)
Radiation dose	
7560 cGy	377 (81.1%)
>7560 cGy	88 (18.9%)
Radiation technique	
IMRT	175 (37.6%)
3DCRT	290 (62.4%)
Race	
White	133 (28.6%)
Black	289 (62.2%)
Hispanic/other	43 (9.2%)
Androgen deprivation	
Yes	192 (41.3%)
No	273 (58.7%)
Radiation field	
Whole pelvis	129 (27.7%)
True pelvis	159 (34.2%)
Prostate/SV	177 (38.1%)

NCCN: National Cancer Care Network; IMRT: intensity-modulated radiation therapy; 3DCRT: 3-dimensional conformal radiation therapy; SV: seminal vesicles.

Kaplan–Meier curves were generated to compare freedom from development of rectal bleeding, and comparisons between groups were made *via* the log-rank test. Univariate and multivariate Cox regression analysis was evaluated for covariates associated with an increased risk of rectal bleeding. The parameters studies included age (continuous), radiation fields (whole pelvis *versus* true pelvis *versus* prostate/seminal vesicles), radiation technique (IMRT *versus* 3DCRT), dose (7560 cGy *versus* >7560 cGy), hormone usage (yes *versus* no), and anticoagulation use (none *versus* aspirin during radiation *versus* clopidogrel/warfarin during radiation *versus* anticoagulation started after radiation). Statistical significance was defined as a *p*-value less than 0.05. All analyses were performed using SPSS, version 21 (IBM Inc, Armonk, NY, USA).

Results

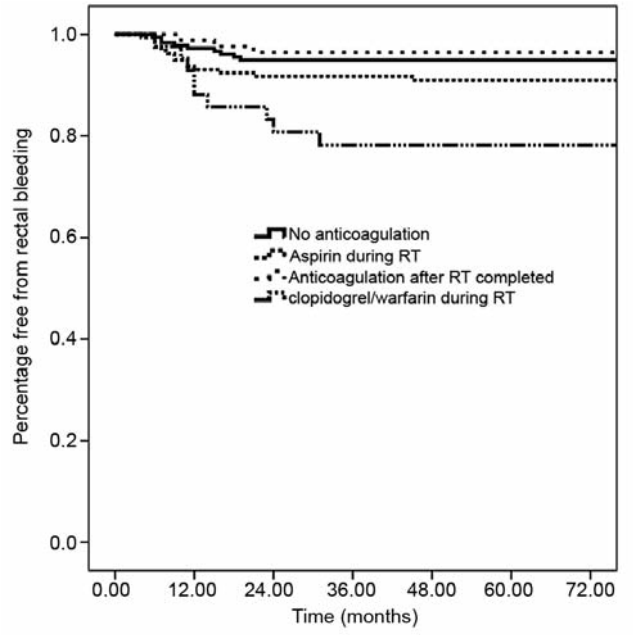
The median follow-up was 70 months (range=11-127) and the median age was 70 years (range=49-86 years). A total of 181 patients (38.9%) were on no anticoagulation at any point. The remaining patients were on some form of anticoagulation during and/or after completion of their radiation treatment. A summary of the anticoagulation is available in Table I. A summary of the patients' characteristics is available in Table II.

There were five patients who developed grade 2 rectal bleeding that resolved either spontaneously or with medical intervention alone. Twenty-seven patients developed grade 3 rectal bleeding that required at least one treatment with argon plasma coagulation to cauterize the bleeding. Three patients developed grade 4 rectal bleeding that required admission to the hospital and blood transfusions. The overall bleeding rate was 7.5%. The median time to rectal bleeding from completion of radiation treatment was 11 months (range=4-45 months). Most bleeding events (94.3%) took place within the first two years after completion of radiation treatment. There were two subsequent bleeding events, one at 31 months and the other at 45 months after completion of radiation treatment. Although the median follow-up was 70 months, there were no bleeding events attributable to the radiation therapy after 45 months.

When comparing bleeding rates based on anticoagulation use at any time, the rate of 4-year freedom from rectal bleeding was 94.7% for those never on anticoagulation *versus* 90.9% for those on anticoagulation (p=0.11).

When looking at anticoagulation use during radiation treatment, we found a significant difference between those who were on aspirin during radiation treatment and those who were on clopidogrel or warfarin during radiation treatment. For those on aspirin, the 4-year freedom from rectal bleeding rate was 91%, which remained statistically unchanged compared to the rate of 94.7% for patients who were never on anticoagulation (p=0.16). For those on warfarin or clopidogrel the 4-year freedom from rectal bleeding rate was 78.2%, which was statistically inferior to the rate of 94.7% in those patients never on anticoagulation (p<0.001).

When looking at anticoagulation use that started after radiation treatment were completed, we again noted no significant differences between the anticoagulation –and no– anticoagulation groups in regards to rectal bleeding. Those who started aspirin after completion of radiation treatment had a 4-year rectal bleeding rate of 94.9%, which was similar to the 94.7% freedom from bleeding in those never on anticoagulation (p=0.99). There were no bleeding events in the patients who started clopidogrel or warfarin after completion of radiation treatment, for a 4-year freedom from bleeding of 100% (p=0.12). Of those who started clopidogrel or warfarin after completion of radiation treatment, the median time to start these medications after the completion of radiation was 34 months (range=1-104 months).



Number at risk

No AC	181	174	160	142	118	97	73
ASA during	158	148	142	132	109	84	60
AC after	84	83	80	77	72	63	54
clopidogrel/warfarin during	42	39	34	27	26	26	24

Figure 1. *Rate of freedom from rectal bleeding and number of men at risk treated with external beam radiation for prostate cancer based on their use and timing of anticoagulation. The use of clopidogrel (Clop) or warfarin (Warf) during radiation therapy was associated with significantly higher bleeding risk (p=0.001) compared to the rest of the men.*

Overall, those taking warfarin/clopidogrel were most likely to have grade 2 or higher rectal bleeding (p=0.001). The overall bleeding rates broken down by timing of anticoagulation use are available in Figure 1.

On univariate and multivariate analysis, use of 3DCRT was associated with reduced likelihood of rectal bleeding. However, use of warfarin and of clopidgrel during radiation treatment were strongly associated with an increased risk of rectal bleeding. Further details are available in Table III.

Discussion

In the present study of 465 patients with a long-term median follow-up of 70 months, we found that most post-radiation rectal bleeding events occurred within 2 years post-radiation, and none occurred beyond 45 months after completion of

Table III. *Univariate and multivariate analysis for rectal bleeding.*

	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age (continuous)	1.03 (0.99-1.08)	0.14	1.03 (0.99-1.07)	0.18
Hormone use				
Yes	1		1	
No	1.05 (0.54-2.07)	0.88	1.10 (0.45-2.65)	0.84
Radiation dose				
7560 cGy	1		1	
>7560 cGy	0.55 (0.19-1.55)	0.26	0.35 (0.12-1.04)	0.06
Radiation field				
Whole pelvis	1		1	
Prostate /SV	1.60 (0.69-3.70)	0.28	1.28 (0.44-3.75)	0.66
True pelvis	1.00 (0.40-2.54)	0.99	1.44 (0.46-4.55)	0.53
Radiation technique				
3DCRT	1		1	
IMRT	0.48 (0.25-0.93)	0.03	3.34 (1.28-8.72)	0.01
Anticoagulation				
None	1		1	
Aspirin during RT	1.80 (0.78-4.15)	0.17	1.69 (0.72-3.97)	0.23
clopidogrel/warfarin during RT	4.48 (1.78-11.28)	0.001	4.84 (1.84-12.68)	0.001
Anticoagulation started after RT	0.69 (0.19-2.55)	0.58	0.78 (0.21-2.91)	0.71

HR: Hazard ratio; 95% CI: 95% confidence interval; SV: seminal vesicles; 3DCRT: three-dimensional conformal radiation therapy; IMRT: intensity-modulated radiation therapy; RT: radiation therapy.

radiation treatment. In addition, we found that those who took clopidogrel or warfarin at the time of their radiation treatment appeared to be at significantly higher risk of development of rectal bleeding, with a 4-year actuarial risk of rectal bleeding of 21.4%. However, aspirin use during radiation and any anticoagulation use after radiation were all associated with a rectal bleeding risk of less than 10%.

The development of telangectiasias in the irradiated rectal mucosa has been reported to be the major pathological change leading to an increased risk of rectal bleeding (12, 13). van Lin *et al*. reported on their endoscopy findings that the appearance of telangectasia generally reached a peak at 1 year and then stayed stable or declined at 2 years (14). This seems to correlate well with the possibility that the telangectasias that form on the rectal wall as a result from the radiation may be at an increased propensity to bleed in those patients who were on a clopidogrel or warfarin, both during and after their radiation treatment due to its anticlotting properties. Both our results, as well as several other studies, have reported that while the risk of bleeding persists for many years after radiation treatment, most cases of rectal bleeding occur within the first 2-2.5 years after completion of radiation therapy (15-17). This also correlates well with our findings that the primary concern with anticoagulation is regarding patients who were already on these medications at the time of their radiation therapy and not those who were started on them at some point after completion of their radiation treatment. In our study, the median time to starting clopidogrel/warfarin after completion of radiation was 34 months, and in only 34% of patients were they started within the first two years, which would theoretically be the time of greatest danger for increased risk of bleeding.

Several prior studies also found a strong correlation between the use of anticoagulation and the risk of bleeding. In a large study by Choe *et al*., the use of clopidogrel or warfarin at any time during or after completion of radiation therapy resulted in a markedly increased risk of both rectal and bladder bleeding (9). Interestingly, in that study, the median follow-up was 48 months, but they felt that the bleeding risk would continue to increase over time. In our study, at a median follow-up of 70 months, we did not note any new bleeding events after 45 months, and most of the events occurred within the first two years. In a second study by Takeda *et al*., the use of anticoagulants/antiaggregants was also associated with a doubling of the bleeding risk from 4.3% to 10.1% (p=0.004) (10). The current study refines these findings by noting that the increased bleeding risk appears primarily in patients who are on these medications at the time of their treatment, but not if they started their anticoagulation afterwards.

One interesting finding in our study was that not only was there not an increased risk of bleeding in those patients who started clopidogrel/warfarin after completion of radiation, but in fact there were no bleeding events at all in these patients. Being that this is a retrospective review, we do not believe any definitive conclusions can be drawn from this, as there may have been a selection bias in place, whereby many of

these patients were not reporting any rectal bleeding in order to be eligible for an anticlotting agent. In addition, given that most patients started their therapy more than 2 years after completion of radiation treatment, this was a selected population of patients who were already highly unlikely to develop rectal bleeding.

An additional interesting finding in our study was that the use of IMRT was also an independent predictor for rectal bleeding, with a HR of 3.34 (95% CI=1.28-8.72, p=0.01) on multivariate analysis. We previously reported an increased rectal toxicity in our cohort of patients during the initial two years that we started our IMRT program (11). In fact, the overall rates of grade 2 or higher rectal bleeding were 5.5% for those receiving three-dimensional conformal radiation therapy and 10.8% in those receiving IMRT. Fortunately, when we switched to image guidance along with IMRT we noted a reduction in the rectal toxicity. In the 36 patients in this study who were treated with image guidance, there was only one grade 2 or higher bleeding event (2.8%). This is more in line with the less than 5% rectal toxicity one would expect in patients being treated with IMRT (18).

In recent years, there has been an increased interest in the use of rectal spacers in an attempt to increase the prostate–rectal interface and thereby reduce toxicity (19). A future prospective study should consider utilizing these rectal spacers prior to initiation of radiation treatment in patients taking clopidogrel or warfarin order to reduce the rectal dose and decrease the likelihood of rectal bleeding. In a study by Prada *et al*. includeing patients receiving low-dose brachytherapy subsequently followed by endoscopic examination, the rate of mucosal damage was significantly reduced in the group that received spacers (5% *versus* 36%, p=0.002) and there was a reduction in rectal bleeding in the spacer group from 12% to 0% (20). Therefore, it leads one to think that the patient population at highest risk for rectal bleeding may be the one to derive the most benefit from this procedure.

In conclusion, patients who are taking clopidogrel or warfarin at the time of their radiation treatment appear to be at significantly higher risk for rectal bleeding. However, those who start anticoagulation afterwards do not appear to need to be concerned that this will lead to a higher rate of rectal bleeding. Further studies should be considered in order to reduce the likelihood of rectal bleeding in patients receiving anticoagulation and high-dose external-beam radiation therapy to the prostate.

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