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Treatment Interruption and Discontinuation in Radiotherapy for Rectal Cancer

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ABSTRACT

Radiotherapy with chemotherapy for rectal cancer reduces local recurrence risk. Of 113 patients (59 male, 54 female) undergoing treatment at New York Presbyterian Hospital, 1998–2007, 6 discontinued radiotherapy; all were female. Females were also more likely to have a treatment interruption (35% vs 12%, $p = .004$). Other factors associated with treatment interruption included adjuvant versus neoadjuvant therapy (OR 14.08, 95%CI 1.55–127.87), use of capecitabine versus 5-fluorouracil (OR 75.90, 95%CI 3.33–>999), and development of any adverse event (OR 20.66, 95%CI 1.76–242.12). While radiotherapy discontinuation was uncommon in our cohort, for unknown reasons, females were more likely to discontinue or interrupt treatment.

INTRODUCTION

Rectal cancer is a common malignancy, with more than 40,000 new cases diagnosed in the United States annually (1). Surgery is the mainstay of treatment for nonmetastatic rectal cancer, but studies have demonstrated that radiotherapy with concurrent chemotherapy reduce the risk of local recurrence when given in either the neoadjuvant or adjuvant setting (2). As such, radiotherapy is considered standard of care for patients with both stages II and III rectal cancer (3).

Despite a growing body of evidence for its use and benefits, and the incorporation of radiotherapy into rectal cancer treatment regimens, the extent to which patients adhere to prescribed radiotherapy regimens is unknown. In one prior study that utilized Medicare claims (4), the completion rate of adjuvant radiotherapy for stages II and III rectal cancer was greater than 90%, and discontinuation of radiotherapy was associated with increased mortality. However, treatment interruption was not measured, and risk factors for incomplete treatment were not ascertained. To determine the rates of treatment interruption and discontinuation, we analyzed a cohort of patients who were prescribed a course of radiotherapy for rectal cancer at our two institutions. Our specific aims were; (a) to quantify the rates of treatment interruption and discontinuation among patients undergoing radiotherapy for rectal cancer; and (b) to identify risk factors for treatment interruption.

Keywords: outcomes research, colorectal & anal cancer, radiation oncology
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METHODS

Institutions

NewYork-Presbyterian Hospital is an academic hospital located in New York City, and is comprised of two medical centers, Columbia University Medical Center and Weill Cornell Medical Center. Each of these two centers has a department of radiation oncology, and appropriate patients with newly diagnosed rectal cancer are referred for evaluation.

Patients

We identified all patients who were prescribed a course of radiotherapy for rectal cancer at NewYork-Presbyterian Hospital, Columbia and Cornell campuses, between January 1, 1998, and December 31, 2007. Patients were identified via manual review of medical records at the radiation oncology departments of the two institutions.

Sociodemographic characteristics of each patient, including age, race, marital status, distance of the patient's residence from the medical center, and insurance status were recorded. Comorbid illness and tobacco history were noted for each patient.

The following data related to the rectal cancer were collected; cancer stage based on endoscopic ultrasound, or, if available, resected specimens; and the administration of chemotherapeutic agents in an adjuvant or neoadjuvant setting. The Institutional Review Boards of the two medical centers approved this study.

Treatment

Sessions of radiotherapy were systematically noted in patients' medical records, and any scheduled or unscheduled interruption was likewise acknowledged, with an accompanying explanation for the interruption. Adverse effects of radiotherapy, including desquamation, diarrhea, or any other symptoms attributed to radiotherapy, were recorded. For our analysis, treatment interruptions were defined as missing three or more consecutive or nonconsecutive prescribed sessions of radiotherapy administration. A previously scheduled pause in therapy, such as on a weekend or holiday, was not counted toward the three days comprising an interruption. Treatment discontinuation was defined as an interruption of radiotherapy without resumption as of the time of the analysis, which was conducted with the shortest follow-up period of 1 year.

Statistical analysis

We compared the sociodemographics, comorbidities, and treatment characteristics of patients who had a treatment interruption to those who completed their radiotherapy course uninterrupted. Chi-square and Fisher exact tests were used to compare proportions between the groups. So as to determine independent predictors of treatment interruption, we used multiple logistic regression (SAS, version 9.1). We included in the models all predictor variables that were significant in the univariate analysis, as well as ethnicity and age. A p value of .05 or less was considered statistically significant.

RESULTS

We identified 113 patients at our two institutions who were prescribed a course of radiotherapy for rectal cancer between the years 1998 and 2007, of whom 67 were from the Columbia campus and 46 were from the Cornell campus. Baseline sociodemographic and clinical data are presented in Table 1. Of the 113 patients, 59 (52%) were male. The mean age was 60.2 years (range 28–100). The median dose of radiotherapy prescribed was 5,040 cGy (range 3,000–5,680, *SD* 288 cGy). The median number of fractions prescribed was 28 (range 10–31, *SD* 2 fractions). Of the 97 patients who were prescribed chemotherapy, 56 (58%) were prescribed monotherapy with either 5-fluorouracil ($n = 42$) or capecitabine ($n = 14$); the remainder were prescribed a combination of agents, most commonly 5-fluorouracil with oxaliplatin.

Of the 113 patients who were prescribed radiotherapy, discontinuation or interruption of treatment occurred in 30 individuals (27%). In all 6 patients (5%) discontinued treatment prior to completion (Table 2). All 6 of these patients (100%) were female, as compared to 48 females out of 107 patients (45%) who completed the prescribed course of radiotherapy ($p = .01$). Significant diarrhea occurred in 3 out of the 6 patients, which was documented as the reason that these patients discontinued treatment. Two patients underwent prolonged hospitalization in the midst of their treatment, resulting in discontinuation; one (patient B) was admitted with a subarachnoid hemorrhage, and another (patient E) developed neutropenic sepsis. In one patient (patient D), the original prescription of 31 fractions was made without the expectation of surgery; when, during the treatment course, the patient and treating physicians decided to proceed with resection, the number of fractions was revised to 28 treatments.

In addition to the 6 patients who discontinued treatment, 24 patients had an interruption in their treatment as defined by three or more missed sessions. The 24 patients who had a treatment interruption had a mean treatment course of 50 days (range 42–70, *SD* 7), compared to a mean treatment course of 39 days (range 14–51, *SD* 4) among those who did not have a treatment interruption. Unadjusted associations of patient characteristics with treatment interruptions are listed in Table 3. Female patients were far more likely than male patients to have a treatment interruption (OR 4.07, 95% CI 1.52–10.92). Other factors significantly associated with treatment interruption in the univariate analysis included; (a) the use of radiotherapy in the adjuvant as opposed to the neoadjuvant setting; (b) the use of oral capecitabine as opposed to intravenous 5-fluorouracil as the chemotherapeutic radiosensitizer; (c) treatment site; and (d) the presence of adverse events in general, or diarrhea or desquamation in particular.

The results of the multivariate analysis are summarized in Table 4. Female sex remained predictive of treatment interruption (OR 12.9, 95% CI 1.82–91.15), as did the use of radiotherapy in the adjuvant setting (OR 14.08 95%CI 1.55–127.87) and the use of oral capecitabine as opposed to intravenous 5-fluorouracil (OR 75.90 95%CI 3.33–>999). The development of any adverse event was associated with treatment interruption (OR 20.66 95% CI 1.76–242.12), but the development of desquamation was paradoxically inversely related to interruption (OR 0.011 95% CI <0.001–0.21). The institution location, which was a significant predictor in the univariate analysis, was no longer significant in the multivariate analysis. Age and ethnicity were not predictive of treatment discontinuation in the univariate or multivariate analysis.

DISCUSSION

In this analysis of patients undergoing radiotherapy for rectal cancer at two institutions, 6 out of 113 (5%) patients did not complete the prescribed course of radiotherapy. All 6 patients who discontinued therapy were female. An additional 24 patients (21%) had an interruption of at least 3 days during their course of radiotherapy. Factors independently associated with treatment interruption included female gender, the use of adjuvant as opposed to neoadjuvant therapy, the use of oral capecitabine as opposed to intravenous 5-fluorouracil, and the development of adverse events.

Table 1. Sociodemographic and disease characteristics of rectal cancer patients seen at the columbia and cornell divisions of NewYork-Presbyterian hospital, 1998–2007, who underwent adjuvant or neoadjuvant radiotherapy for resectable rectal cancer

Characteristic	Number of Patients (%)
Total	113
Age ≥65 years	47 (42)
Male	59 (52)
Hospital	
Columbia	67 (59)
Cornell	46 (41)
Race (%)	
Caucasian	54 (48)
Black	20 (18)
Hispanic	36 (32)
Other	3 (3)
Marital Status	
Married	61 (54)
Divorced/Separated/Widowed	52 (46)
Residence[a]	
Local	20 (18)
Distant	93 (83)
Insurance	
Medicaid	26 (23)
Nonmedicaid	87 (77)
Medical comorbidities	
Hypertension	36 (39)
Diabetes	14 (15)
Timing of radiotherapy	
Neoadjuvant	82 (73)
Adjuvant	29 (26)
Chemotherapy	
5-Fluorouracil	72 (69)
Capecitabine	25 (24)
Oxaliplatin	31 (29)
None or unspecified	16 (14)
Cancer stage	
I	17
II	42
III	48
IV	6

[a]Local residence was defined as presiding in a region corresponding to the same ZIP code as the medical center (Cornell, Columbia), or in one of three ZIP codes adjacent to the medical center (Columbia).

Adherence to treatment prescription in oncology has been established as a major factor in determining patient outcomes. For certain chemotherapy regimens, early termination is both common and of major clinical significance. In one database-derived cohort, for example, more than 30% of patients with stage III colon cancer terminated their chemotherapy courses early, and the mortality rate in this group was double compared to patients who completed their chemotherapy course (5). In a cohort of patients with breast cancer, 28% of patients received fewer cycles of chemotherapy than expected, and this phenomenon was associated with both black race and poorer survival (6). These findings indicate that adherence to therapy affects cancer outcomes.

In contrast, completion rates of prescribed radiotherapy regimens usually appear to be generally high. In an analysis of the Surveillance, Epidemiology, and End Results (SEER)-Medicare database for the years 1991–1999 (7), only 3% of 7,791 patients with early stage breast cancer failed to complete their prescribed dose of radiotherapy. Nevertheless, failure to complete this course was associated with an increased odds of death. Low rates of discontinuation were also observed in a SEER-Medicare study of radiotherapy of rectal cancer, the only previous study of radiotherapy adherence in rectal cancer to date (4). In that analysis, discontinuation occurred in 8.5% and 3.4% of patients with stage II and stage III rectal cancer, respectively. While discontinuation was associated with increased mortality, risk factors for discontinuation were not assessed, and treatment interruption (with ultimate completion) was not considered.

The rate of treatment discontinuation in our cohort was similarly low, with 6 of 113 (5%) patients failing to complete the prescribed course of radiotherapy. All 6 patients who discontinued radiotherapy were female, and female gender was strongly associated with treatment interruption in univariate as well as multivariate analysis. The reasons for this phenomenon are obscure. Differences in pelvic anatomy or a gender-specific adverse response profile may contribute to this phenomenon. For example, female patients may be more severely affected by moist desquamation, as desquamation in the vulvar region may be less tolerable than scrotal irritation. However, this marked difference

Table 2. Characteristics of the six patients who did not complete the prescribed course of radiotherapy of rectal cancer patients seen at the Columbia and cornell divisions of NewYork-Presbyterian hospital, 1998–2007, who underwent adjuvant or neoadjuvant radiotherapy for resectable rectal cancer

Patient	Age	Sex	Ethnicity	Proximity to Medical Center	Stage	Comorbidities	Timing of Chemoradiation	Type of Chemotherapy	Fractions Prescribed	Fractions Administered	Adverse Events
A	75	F	W	distant	I	depression	adjuvant	5FU	31	16	diarrhea, radiation enteritis
B	54	F	H	local	IIA	bipolar disorder	neoadjuvant	5FU	28	9	neutropenic sepsis
C	80	F	W	distant	I	hypertension, prior colon cancer at hepatic flexure	adjuvant	5FU	28	21	diarrhea
D	46	F	H	distant	I	none	neoadjuvant	5FU, Oxaliplatin	31	28	moist desquamation
E	68	F	H	local	IIB	hypertension, diabetes	adjuvant	5FU	25	4	moist desquamation
F	68	F	W	distant	IIIB	diabetes, coronary artery disease	neoadjuvant	5FU	28	20	diarrhea

Table 3. Unadjusted associations of patient characteristics with treatment interruption, among all patients who completed a course of radiotherapy ($n = 107$) of rectal cancer patients seen at the Columbia and cornell divisions of NewYork-Presbyterian hospital, 1998–2007, who underwent adjuvant or neoadjuvant radiotherapy for resectable rectal cancer

Characteristic	Percentage with Interruption	*p* value
Age		.95
≥65	23 (10/44)	
<65	22 (14/63)	
Sex		.004
Male	12 (7/59)	
Female	35 (17/48)	
Ethnicity		.1
Caucasian	29 (15/51)	
NonCaucasian	16 (9/56)	
Marital status		.298
Married	19 (11/59)	
Divorced/separated/widowed	27 (13/48)	
Residence		.55
Local	28 (5/18)	
Distant	21 (19/89)	
Insurance status		.45
Medicaid	28 (7/25)	
NonMedicaid	21 (17/82)	
Hospital		.02
Columbia	15 (9/62)	
Cornell	33 (15/45)	
Medical comorbidities		
Hypertension	18 (6/34)	.42
Diabetes	17 (2/12)	1.0
Cancer stage		.44
I	14 (2/14)	
II	18 (7/40)	
III	30 (14/47)	
IV	17 (1/6)	
Timing of radiotherapy		.03
Adjuvant	38 (10/26)	
Neoadjuvant	17 (14/79)	
Type of chemotherapy		
5-Fluorouracil	15 (10/67)	.003
Capecitabine	50 (12/24)	.0002
Oxaliplatin	21 (6/29)	.74
Adverse events		
Any	29 (20/70)	.04
Desquamation	8 (3/37)	.01
Diarrhea	48 (12/25)	.0005

Table 4. Multivariate logistic regression for predictors of treatment interruption among all patients who completed a course of radiotherapy ($n = 107$) of rectal cancer patients seen at the Columbia and cornell divisions of NewYork-Presbyterian hospital, 1998–2007, who underwent adjuvant or neoadjuvant radiotherapy for resectable rectal cancer. 5FU: 5-fluorouracil

Characteristic	Odds Ratio	95% Confidence Interval	*p* value
Age	0.99	0.93–1.04	.64
Female	12.9	1.82–91.15	.01
Caucasian	5.17	0.82–32.77	.08
Columbia as opposed to Cornell	7.65	0.64–91.66	.11
Adjuvant chemotherapy	14.08	1.55–127.87	.02
Capecitabine as opposed to 5FU	75.90	3.33– > 999	.0066
Development of any adverse event	20.66	1.76–242.12	.016
Development of desquamation	0.011	< 0.001–0.21	.0025
Development of diarrhea	2.08	0.275–15.71	.48

remained after controlling for several specific adverse effects, including desquamation and diarrhea. This disparity mandates replication and further analysis of comorbidities and treatment-related adverse events so as to generate hypotheses for this association.

Explanations for the remaining predictors of treatment interruption are more obvious. Patients receiving radiotherapy in an adjuvant setting may be at greater risk for treatment interruption due to a postoperative reduction in functional status. Another possible reason for the difference in interruption rates between adjuvant and neoadjuvant therapy is that patients receiving radiotherapy in the neoadjuvant setting have a more tangible incentive to complete their course promptly, as this will lead to definitive surgical therapy. This latter explanation, though plausible, has not been previously cited as a benefit of neoadjuvant as opposed to adjuvant therapy for rectal cancer.

The association between capecitabine use as opposed to 5-fluorouracil and treatment interruption may be understood as a reflection of a more frail patient group opting for oral chemotherapy; such patients may be more susceptible to treatment interruption due to this underlying difference in performance status.

As expected, the development of adverse events in general was associated with treatment interruption. However, desquamation was paradoxically associated with a decreased odds of treatment interruption. Such an association is unexpected, and is unlikely to be causal. A more plausible explanation for the observed findings is that patients who had a treatment interruption were less likely to have desquamation, since the interruption allowed the opportunity for the skin to recover from incipient radiation injury.

This study has a number of limitations. Clinical endpoints, such as disease recurrence, disease-specific mortality, and overall mortality, were not available, raising the question of the clinical significance of treatment interruption. However, multiple studies of a range of malignancies, have demonstrated that interruption of radiotherapy is associated with an increased risk of cancer recurrence and death (8–13). Our study was limited to two academic institutions in one city, raising the question of generalizability, although the rate of treatment discontinuation was similar to that found in a large Medicare database study (4). Information regarding medical comorbidities was limited to diabetes and hypertension, and did not include depression, which may be common in a cohort of patients with a recent diagnosis of cancer (14), and which may impact patients' adherence to the prescribed course of therapy. A composite score of patients' performance status was likewise unavailable. As this metric is associated with chemotherapy discontinuation in colon cancer (5), there is reason to suspect that performance status affects radiotherapy interruption or discontinuation.

In conclusion, in this first study measuring both treatment interruptions and discontinuation in patients undergoing radiotherapy for rectal cancer, female patients were far more likely to have a treatment interruption than male patients. Other variables associated with treatment interruption included the use of oral capecitabine as opposed to intravenous 5-fluorouracil chemotherapy, adjuvant rather than neoadjuvant radiotherapy, and the development of adverse events related to radiotherapy. Future studies are warranted to investigate the implications of radiotherapy interruption on rectal cancer recurrence and mortality, and to further elucidate the association of female gender with treatment interruption and discontinuation.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. B. Lebwohl is supported by a fellowship from the National Cancer Institute (T32-CA095929).

REFERENCES

1. Jemal, A.; Siegel, R.; Ward, E.; Hao, Y.; Xu, J.; Murray, T.; Thun, M.J. Cancer statistics, 2008. CA Cancer J Clin **2008**, *58*, 71–96.
2. Nagy, V.M. Updating the management of rectal cancer. J Gastrointestin Liver Dis **2008**, *17*, 69–74.
3. Desch, C.E.; McNiff, K.K.; Schneider, E.C.; Schrag, D.; McClure, J.; Lepisto, E.; Donaldson, M.S.; Kahn, K.L.; Weeks, J.C.; Ko, C.Y.; Stewart, A.K.; Edge, S.B. American society of clinical oncology/national comprehensive cancer network quality measures. J Clin Oncol **2008**, *26*, 3631–3637.
4. Dobie, S.A.; Warren, J.L.; Matthews, B.; Schwartz, D.; Baldwin, L.M.; Billingsley, K. Survival benefits and trends in use of adjuvant therapy among elderly stage II and III rectal cancer patients in the general population. Cancer **2008**, *112*, 789–799.
5. Neugut, A.I.; Matasar, M.; Wang, X.; McBride, R.; Jacobson, J.S.; Tsai, W.Y.; Grann, V.R.; Hershman, D.L. Duration of adjuvant chemotherapy for colon cancer and survival among the elderly. J Clin Oncol **2006**, *24*, 2368–2375.
6. Hershman, D.; McBride, R.; Jacobson, J.S.; Lamerato, L.; Roberts, K.; Grann, V.R.; Neugut, A.I. Racial disparities in treatment and survival among women with early-stage breast cancer. J Clin Oncol **2005**, *23*, 6639–6646.
7. Gold, H.T.; Do, H.T.; Dick, A.W. Correlates and effect of suboptimal radiotherapy in women with ductal carcinoma in situ or early invasive breast cancer. Cancer **2008**, *113*, 3108–3115.
8. Weber, D.C.; Kurtz, J.M.; Allal, A.S. The impact of gap duration on local control in anal canal carcinoma treated by split-course radiotherapy and concomitant chemotherapy. Int J Radiat Oncol Biol Phys **2001**, *50*, 675–680.
9. Videtic, G.M.; Fung, K.; Tomiak, A.T.; Stitt, L.W.; Dar, A.R.; Truong, P.T.; Yu, E.W.; Vincent, M.D.; Kocha, W.I. Using treatment interruptions to palliate the toxicity from concurrent chemoradiation for limited small cell lung cancer decreases survival and disease control. Lung Cancer **2001**, *33*, 249–258.
10. Kwong, D.L.; Sham, J.S.; Chua, D.T.; Choy, D.T.; Au, G.K.; Wu, P.M. The effect of interruptions and prolonged treatment time in radiotherapy for nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys **1997**, *39*, 703–710.
11. Barton, M.B.; Keane, T.J.; Gadalla, T.; Maki, E. The effect of treatment time and treatment interruption on tumour control following radical radiotherapy of laryngeal cancer. Radiother Oncol **1992**, *23*, 137–143.
12. Srokowski, T.P.; Fang, S.; Duan, Z.; Buchholz, T.A.; Hortobagyi, G.N.; Goodwin, J.S.; Giordano, S.H. Completion of adjuvant radiation therapy among women with breast cancer. Cancer **2008**, *113*, 22–29.
13. Bese, N.S.; Sut, P.A.; Sut, N.; Ober, A. The impact of treatment interruptions on locoregional control during postoperative breast irradiation. J BUON **2007**, *12*, 353–359.
14. Massie, M.J. Prevalence of depression in patients with cancer. J Nat Cancer Inst Monogr **2004**, *32*, 57–71.