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Differential effects of patient-related factors on the outcome of radiation therapy for rectal cancer

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Abstract

Objective—The objective of this study was to investigate whether cancer specific survival in rectal cancer patients is affected by patient-related factors, conditional on radiation treatment.

Methods—359 invasive rectal cancer patients who consented and provided questionnaire data for a population-based case-control study of colorectal cancer in Metropolitan Detroit were included in this study. Their vital status was ascertained through to the population-based cancer registry. Hazard ratios (HR) for cancer specific and other deaths and 95% confidence intervals (CIs) were calculated according to selected patients' characteristics, stratified by radiation status, using joint Cox proportional hazards models.

Results—A total of 159 patients were found to be deceased after the median follow-up of 9.2 years, and 70% of them were considered to be cancer specific. Smoking and a history of diabetes were associated with an increased probability of deaths from other causes (HR 3.20, 95% CI 1.72–5.97 and HR 2.02, 95% CI 0.98–4.16, respectively), while regular use of non-steroidal anti-inflammatory drugs (NSAIDs) was inversely correlated with cancer-specific mortality (HR 0.50, 95% CI 0.30–0.81). Furthermore, the associations of smoking and NSAIDs with the two different types of deaths (cancer vs others) significantly varied with radiation status (P-values for the interactions= 0.014 for both). In addition, we observed a marginally significantly reduced risk of

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Conflict of Interest statement:

Ikuko Kato declares no conflicts of interest.

Gregory Dyson declares no conflicts of interest.

Michael Snyder declares no conflicts of interest.

Hyeong-Reh Kim declares no conflicts of interest.

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Statement of Ethical standards: The study has been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All persons gave their informed consent prior to their inclusion in the study.

cancer specific deaths in the patients who had the relative ketogenic diet overall (HR=0.49, 95% 0.23–1.02).

Conclusion—Further research is warranted to confirm these results in order to develop new interventions to improve outcome from radiation treatment.

Keywords

Non-steroidal anti-inflammatory drugs; smoking; diet; rectal cancer; survival

Introduction

The treatment of rectal cancer has evolved significantly during the past few decades and radiation is now part of the standard protocol for rectal cancer management [1–3]. It is primarily given for stage 2 and 3 cases as neo-adjuvant therapy before surgery, with or without concomitant administration of chemotherapeutic agents. Introduction of these preoperative treatments along with better surgical techniques have been ascribed to recent improvements in overall survival from rectal cancer at the population level [4–6] as well as to improved quality of life by allowing more sphincter preserving surgeries [7,8]. Yet, local and distant recurrences occur in a fraction of the patients. Several tumor related factors, including tumor size, tumor location, and local extension, and other treatment-related factors, such as negative surgical margin, radiation dose, and pathological response to radiation, concomitant chemotherapy use and type of agents used, have been associated with local recurrence and survival [1,2,9]. In addition, systemic markers, CEA and pro-inflammatory reactants, such as CRP and neutrophil count, have been shown to predict outcome of neoadjuvant radiation [10,11]

Biophysically, hypoxic lesions and tumors with increased anaerobic glycolysis are known to be radioresistant [12,13]. There are a number of pharmacological modifiers which alleviate hypoxia and correct aberrant tumor metabolism by reducing glycolysis and enhancing mitochondrial oxidation [12,13]. Many of these compounds are already in clinical use or testing for cancer and other conditions [14,15]. In addition, human lifestyle and behavioral factors possibly modulate these pathways. Short term starvation and ketogenic diets, which lead to lower availability of glycolysis substrate, have been demonstrated to enhance the effect of radiation treatment in mouse glioma models [16,17]. Smoking may cause a low-grade chronic hypoxic condition due to elevated carbon monoxide levels and pharmacological actions of nicotine [18,19]. Some over the counter medications such as Aspirin and Ibuprofen are known to act on these pathways [20,14].

To date, there has been minimal study of whether these patient-related factors indeed modify outcome of radiation treatment for rectal cancer patients. Leveraging the data collected for a population-based case-control study of colorectal cancer in Metropolitan Detroit, and survival linkage to its population-based cancer registry, we sought to address whether cancer specific survival in rectal cancer patients is affected by their medical history and lifestyle factors, conditional on radiation treatment. We focus on patients' factors that potentially intervene in the atmospheric and nutritional environments of a tumor, namely smoking,

medications and body composition and macronutrient intake, based on the literature review cited above and others.

Methods

Study subjects and data acquisition

The subjects for this study were derived from rectal cancer cases who were enrolled in a population-based case-control study of colorectal cancer in Metropolitan Detroit, details of which have been reported elsewhere [21,22]. The study was approved by the Wayne State University Human Investigation Committee. Eligible cases were diagnosed between January 1, 2003 and September 30, 2005, were histologically confirmed, were and between 45 and 80 years of age, and were identified through the Metropolitan Detroit Cancer Surveillance System (MDCSS), which is a founding member of National Cancer Institute supported Surveillance Epidemiology and End Results (SEER) Program. There were 359 invasive rectal cancer cases among the 1163 final eligible colorectal cancer patients that consented and provided valid questionnaire data to the parent study. At enrolment, the study participants were interviewed over the telephone using structured questionnaires regarding their usual diet and other risk factors for colorectal cancer for the time-period preceding cancer diagnosis (approximately 2 years prior to the interview) to rule out influences of the disease, and provided a biospecimen for genotyping assays. A validated semi-quantitative food frequency questionnaire, Block 98.2 (Block Dietary Data Systems, Berkeley, CA), was used to estimate daily nutrient (including individual fatty acid groups) intake. Energy-adjusted nutrient intake was calculated by means of the residual method [23]. Participants were also queried about regular use of selected common medications, which was defined as at least 3–4 times per week for 6 months or longer. Body mass index (kg/m²) and physical activity (weighted sum of time the subject spent per 24 hours) were calculated as described previously [21,22]. Smoking and alcohol use status was dichotomized, current smoker vs not and daily alcohol drinker vs not, respectively. Information concerning clinical and histological characteristics of tumor, vital status (as of July 1, 2014) and cause of death was obtained through linkage with MDCSS. Causes of deaths (ICD10) were divided into two groups, cancer specific (cancers of the intestinal tract, liver and unknown primary sites) or other deaths according to one of the site-specific schemes for cause-specific deaths used in SEER program. The classification was made without knowledge of patients' radiation therapy status.

Statistical analysis

We adopted the joint Cox proportional hazards models proposed by Xue et al [24] for evaluating multiple outcomes in prospective cohort studies to analyze simultaneously cancer specific deaths and other deaths. This model was originally proposed for the analysis of competing risk events [25]. Hazard ratios (HR) for deaths and 95% confidence intervals (CIs) were calculated according to selected patients' characteristics, and were adjusted for age, sex and stage of the disease, for all patients, patients treated by radiation and those not treated by radiation. These basic covariates were screened from those associated with overall survival at least at $p < 0.10$ level. Continuous covariates were grouped into quintiles based on distributions of the cases and controls combined to calculate HRs compared with the lowest

quintile (the reference category). We performed tests for linear trend in HRs for these variables using ordinal scores for each category. Furthermore, we tested the interactions between radiation treatment and these ordinal or binary covariates by including their multiplicative interaction terms. A difference in the HRs between two groups of the events was tested based on their regression coefficients and standard errors using a Z test. All statistical analyses were performed using SAS version 9.2.

Results

38% (137 out of 359) of the patients received radiation treatment as part of the initial course of cancer targeted therapy (Table 1). Among those who had also surgical resection (N=121), 49% had radiation preoperatively and 54% had postoperatively (3% for both) (data not shown). Most (92%) of the patients treated with radiation also received chemotherapy and the patients treated with radiation were diagnosed at more advanced stage than those without radiation ($P<0.01$). A total of 159 patients were found to be deceased after the median follow-up of 9.2 years, and 70% of them were considered to be cancer specific.

Smoking and a history of diabetes were associated with an increased probability of deaths from other causes (HR 3.20, 95% CI 1.72–5.97 and HR 2.02, 95% CI 0.98–4.16, respectively), while there were no associations between these two factors and cancer specific death. On the other hand regular use of non-steroidal anti-inflammatory drugs (NSAIDs) was inversely correlated with cancer-specific mortality (HR 0.50, 95% CI 0.30–0.81). As a result, the HRs associated with these three factors were significantly different from cancer specific to other deaths ($P=0.019$, 0.015 and 0.041, respectively). There were no overall associations of any of the nutritional factors or physical activity with either type of outcomes (Table 2).

We further analyzed the data, stratified by radiation therapy status. As illustrated in Fig 1, among the patients who were irradiated, smoking tended to increase cancer specific deaths but to reduce other deaths, while the increased risk of deaths from other causes associated with smoking was apparent among those not irradiated (HR=6.01 95% CI 2.82–12.78). The HR for cancer specific deaths was significantly reduced in only the regular NSAID users who had radiation (HR=0.41 95% CI 0.21–0.81), compared with non-users with radiation, which was also significantly different ($P=0.005$) from the corresponding HR for other deaths in the patients who were irradiated (2.68, 95% CI 0.89–8.08). The association of these two factors (smoking and NSAIDs) with the two different types of deaths (cancer vs others) significantly varied with radiation status (P -values for the interactions= 0.014 for both). Further adjustment of these two factors each other did not change the significance of the associations (data not shown). There were no monotonic increasing or decreasing trends in risk of either type of deaths with any nutritional factor by radiation status. However, among the patients with radiation therapy, cancer specific HR was decreased with higher calories from fat (top vs bottom HR 0.63 95% CI 0.26–1.53), while that for other deaths was reduced with high glycemic load (top vs bottom HR 0.19, 95% CI 0.02–1.66).

We also analyzed whether a relative ketogenic diet, defined as $\geq 40\%$ calorie from fat and $<100\text{g/day}$ glycemic load based on overall distributions, influences the outcome of radiation

therapy (Table 3). We observed a marginally significantly reduced risk of cancer specific death in the patients who had the relative ketogenic diet overall (HR=0.49, 95% 0.23–1.02). Although the cancer specific HR associated with the ketogenic diet differed minimally by radiation treatment status, it was significantly lower than the corresponding HR for other deaths in the irradiated group only (P= 0.025).

Discussion

The results of the present study demonstrate that some patient-related factors may exert disparate effects on cancer specific deaths and other deaths. Furthermore, their effects varied appreciably by radiation treatment status, suggesting a possibility that such patient-related factors may alter radiation sensitivity or radiation toxicity. These observations may have clinical translational value as such patient-related factors are modifiable, as opposed to tumor characteristics.

In our study population, smoking was associated with an increased risk of non-cancer specific deaths. Although cigarette smoking has been convincingly associated with an increased risk of colorectal neoplasms, the association with colorectal cancer itself has been rather modest, compared with more pronounced association with adenoma [26–28], suggesting a role in earlier stage of carcinogenesis. In contrast, smoking has been more firmly linked to other causes of deaths, such as cardiovascular diseases and respiratory diseases including lung cancer [29]. The fact that these causes of deaths comprised a substantial proportion (~50%) of non-cancer specific deaths is likely to account for the observed association.

Data from both observational studies and clinical trials suggest that regular NSAID and aspirin use reduces not only cancer incidence but also cancer mortality [30,31]. The evidence has been particularly strong and consistent for colorectal cancer, as these drugs have been demonstrated to reduce the risk of polyp recurrence as well as the incidence and mortality of colorectal cancers [30]. Although the preventive effects on cancer incidence and mortality are generally seen after a latent period of about 10 years [32], recent studies have highlighted their potential short term benefits on cancer incidence, death, survival and risk of metastasis [31,33–35]. Thus, reduced risk of cancer specific mortality observed in our study is consistent with these observations.

Interestingly, these two personal exposures had differential effects on cancer-specific and other deaths depending on radiation therapy status. Hypoxic cells are not only resistant to radiation because of low oxygen level per se, but also induce angiogenesis and fibrosis, as well as are important selective force in the progression of cancer, i.e., local invasion and distant metastasis [36–39]. These pathophysiological changes are mediated by a nuclear transcriptional regulator, hypoxia-inducible factor (HIF) [37,38]. Accordingly, over-expression of HIF-1 α and other hypoxia-responsive genes has been associated with increased risk of treatment failure and recurrence and reduced overall and disease-free survival [40–44]. Not only does smoking cause a low-grade hypoxia due to elevated carbon monoxide levels [18], but also nicotine induces HIF-1 α expression leading to radioresistance in a lung cancer xenograft model [19].

HIF-1 α activation leads to the change in tumor energy metabolism from mitochondrial respiration to anaerobic glycolysis which is considered a hallmark of cancer in order to meet increased energy need for rapid cell proliferation (so called Warburg Effect) [45,46] and, metabolic intermediates of the glycolytic pathway, such as lactate and pyruvate, also confer radioresistance and promote tumor progression [47,12]. Aspirin and Ibuprofen, commonly used NSAIDs, interfere with these pathways, through inhibition of key enzymes, such as mTOR and COX2 [20,14]. These are potential underlying mechanisms may account for the suggestive association of smoking and NSAIDs use with cancer specific mortality that appeared to be more pronounced in the patients who underwent radiation.

A growing body of evidence also supports the suggestion that ketogenic conditions (via short term starvation or high fat/low carbohydrate diet) are useful to target the Warburg Effect by limiting a substrate for anaerobic glycolysis [48], and thus deter tumor progression/proliferation [15,12] and potentiate the effects of radiation or chemoradiation therapies in animal models [16,17]. Therapeutic ketogenic diets typically prescribed for epilepsy use a very fat/carbohydrate plus protein ratio, i.e., 4:1 [17], beyond regular weight loss diets, and thus was not translatable to our study population. Instead, we defined a relative ketogenic diet based on overall distribution of percent fat and glycemic loads. Even so, our data were supportive for the potential effects of ketogenic diet in reducing cancer specific mortality.

The strengths of the study include the population-based study design, high quality follow-up [49], sufficient follow-up time to identify a substantial number of cancer specific mortalities, use of a competing risk model and a variety of personal exposure data which are usually not available for clinical samples. On the other hand we realize several limitations. First, survival bias may be a concern as patients who succumbed quickly were not able to be included in the study as the case ascertainment through MDCSS followed by physician notification processes took 3–5 months from diagnosis and because patients who are gravely ill or on continuous treatment are generally unwilling to participate. This may have lowered the proportion of the patients with aggressive tumor or advanced stage, for which radiation treatment may be more often prescribed and thus may have resulted in biased estimates if such patients differed from those who participated in the study in the personal characteristics associated with cancer specific mortality. Second, we acknowledge that the classification of causes of death has influences on the results of the analyses and that there was some room for misclassification due to a lack of access to medical records. Deaths from complication from radiation toxicity could have been misclassified as non-cancer specific death. However, even if patients who were radiosensitive due to a certain characteristic suffered from such a complication, this should have led to a weakening of the interaction, rather than strengthening. Also, as is the nature of observational studies, we acknowledge that uncontrolled differences exist between patients who were treated by radiation and those who were not concerning a number of unmeasured variables, which may be confounded in the observed associations, and that the findings may not be considered to be as clear-cut or definitive as those from clinical trials. Furthermore, the parent study was designed to explore etiological risk factors of colorectal cancer, and consequently exposure data we collected reflect those before cancer diagnosis which could change after diagnosis and during treatment.

The present study was based on a posteriori analysis and involves multiple comparisons. Thus, we realize that some of the results may be simply a chance finding and a caution should be exercised in the interpretation of the results. In addition, when patients were grouped according to cause of deaths, radiation status and personal characteristics, the numbers of the patients and events in each stratum became considerably small. This may result in inaccurate risk estimates with wide confidence intervals and also restricted the number of covariates to be included in the statistical models. Finally, we are aware that other statistical models for competing risks in survival analysis exist [50,51], but the model used here has been considered to provide directly comparable risk estimates across all types of outcomes included.

Conclusions

Despite these limitations, this study provides novel observations that corroborate laboratory data and are potentially clinically useful to improve outcomes from radiation treatment if they are validated. Thus, the insights gained from this study may possibly lead to higher efficacy of radiotherapy in future patients by means of life-style modifications, which has been proven to be a cost effective intervention. Confirmatory prospective studies are necessary, including a larger sample size, better exposure assessment and more clearly defined patient populations, in order to develop new intervention protocol to be tested in clinical trials.

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Fig. 1.

Hazard ratios (HRs) for cancer specific deaths and for other deaths associated with smoking and non-steroidal anti-inflammatory drugs (NSAIDS) use status, stratified by history radiation therapy (striped bars: no radiation, solid bars: radiation). The extended lines from the top of the bars indicate 95% confidence intervals. The "n" in the parentheses indicates the numbers of each event for no radiation and radiation groups and the p-values in the parentheses those for the interactions between smoking/NSAIDS with radiation therapy status and causes of deaths.

Table 1

Characteristics of 359 rectal cancer patients enrolled in an epidemiologic study by radiation therapy status

Characteristics	No radiation therapy (N=222)		Radiation therapy (N=137)		
	No.	(%)*	No.	(%)*	
Age	45–49	17	8%	11	8%
	50–54	49	22%	27	20%
	55–59	38	17%	28	20%
	60–64	25	11%	22	16%
	65–69	31	14%	16	12%
	70–74	28	13%	20	15%
sex	75–80	34	15%	13	9%
	Female	109	49%	63	46%
Race	Male	113	51%	74	54%
	African	63	28%	21	15%
	Other	159	72%	116	85%
Cancer stage	Local/regional	154	69%	68	50%
	Node or distant metastasis	68	31%	69	50%
Surgery	No	25	11%	16	12%
	Local excision	59	27%	15	11%
	Segmental resection	114	51%	65	47%
Chemotherapy	Proctectomy	24	11%	41	30%
	No	185	83%	11	8%
	Received	37	17%	126	92%
Vital status	Alive	132	59%	68	50%
	Died of cancer	59	27%	53	39%
	Died of other causes	31	14%	16	12%

^{*} column percentages within groups (no radiation or radiation)

Hazard ratio (HR) and 95% confidence interval (CI) for cancer specific and other deaths associated with selected patient characteristics

Table 2

Patient characteristics	Patients	Cancer specific death			Other death		
		Events	HR	95% CI	Events	HR	95% CI
Smoking status							
No	281	84	1.00		31	1.00	
Yes	77	28	1.25*	0.79–1.98	16	3.20*	1.72–5.97
Alcohol							
Not daily	280	90	1.00		33	1.00	
Daily	79	22	0.76	0.45–1.27	14	1.61	0.85–3.03
Non-steroidal anti-inflammatory drugs							
No	245	89	1.00		28	1.00	
Used	114	23	0.50*	0.30–0.81	19	1.11*	0.61–2.02
Diabetes							
No	313	100	1.00		36	1.00	
Ever	46	12	0.66*	0.37–1.18	11	2.02*	0.98–4.16
Physical activity index							
<27.14	71	33	1.00		9	1.00	
27.14–28.6	73	23	0.80	0.45–1.40	11	1.22	0.50–2.99
28.6–30.5	71	16	0.63	0.35–1.15	13	1.57	0.68–3.63
30.6–34.5	72	16	0.52	0.27–0.99	8	0.94	0.37–2.44
>34.5	72	24	0.94	0.52–1.69	6	0.74	0.26–2.10
Trend				P=0.397			P=0.490
BMI (kg/m ²)							
<23.76	71	24	1.00		8	1.00	
23.77–25.85	72	23	1.06	0.60–1.88	11	1.93	0.78–4.78
25.86–28.4	72	19	0.67	0.36–1.27	9	1.09	0.42–2.86
28.5–32.55	72	22	0.69	0.38–1.28	10	1.09	0.42–2.85
>32.56	72	23	0.99	0.57–1.73	9	1.36	0.53–3.53
Trend				P=0.526			P=0.992
Calories (kcal/day)							
<1490	71	22	1.00		13	1.00	
1490–1940	72	21	1.18	0.63–2.22	7	0.65	0.25–1.72
1941–2450	72	22	1.19	0.64–2.18	9	0.88	0.38–2.05
2451–3080	72	20	0.85	0.44–1.65	9	0.91	0.38–2.18
>3081	72	27	1.44	0.74–2.79	9	1.10	0.43–2.79
Trend				P=0.592			P=0.746
% fat							
<32.0	71	23	1.00		11	1.00	

Patient characteristics	Cancer specific death				Other death			
	Patients	Events	HR	95% CI	Events	HR	95% CI	
% carbohydrate	32.0–36.1	72	28	1.36	0.76–2.46	11	1.18	0.50–2.75
	36.2–39.6	72	28	1.71	0.96–3.05	9	1.09	0.44–2.68
	39.7–42.7	72	15	0.78	0.41–1.50	8	0.80	0.32–2.02
	>42.8	72	18	0.85	0.45–1.60	8	0.82	0.32–2.13
	Trend			P=0.246			P=0.475	
	<40.3	71	16	1.00		10	1.00	
	40.3–44.8	72	21	1.48	0.75–2.92	8	0.86	0.33–2.23
	44.9–49.1	72	23	1.69	0.88–3.25	11	1.10	0.47–2.57
	49.2–53.9	72	26	1.69	0.86–3.32	6	0.51	0.18–1.47
	>=54.0	72	26	1.55	0.78–3.08	12	1.02	0.41–2.54
Glycemic load (g/day)	Trend			P=0.202			P=0.772	
	<84.5	71	19	1.00		8	1.00	
	84.6–109.6	72	23	1.18	0.61–2.28	12	1.61	0.66–3.92
	109.7–145	72	22	0.96	0.51–1.82	10	1.37	0.55–3.40
	145.5–183	72	17	0.86	0.43–1.70	8	1.09	0.42–2.85
	>=183	72	31	1.61	0.86–3.03	8	1.52	0.57–4.08
Trend			P=0.303			P=0.726		

HR: adjusted for age, sex and stage, based on joint Cox proportional hazards models

* HRs significantly differed between cancer specific and other deaths (p<0.05)

Table 3

Hazard ratio (HR) and 95% confidence interval (CI) for cancer specific and other deaths associated with ketogenic diet by radiation therapy status

Patient groups	Diet type	Patients	Cancer specific death			Other death		
			Events	HR	95% CI	Events	HR	95% CI
All patients	Non-ketogenic diet	311	104	1.00		41	1.00	
	Ketogenic-diet	48	8	0.49	0.23–1.02	6	0.80	0.34–1.87
No radiation	Non-ketogenic diet	192	55	1.00		29	1.00	
	Ketogenic-diet	30	4	0.49	0.16–1.49	2	0.35	0.08–1.52
Radiation	Non-ketogenic diet	119	49	1.00		12	1.00	
	Ketogenic-diet	18	4	0.47*	0.18–1.27	4	2.52*	0.82–7.69
Interaction of ketogenic diet with radiation and cause of deaths								
P=0.111								

Ketogenic diet was defined as $\geq 40\%$ calorie from fat and $< 100\text{g/day}$ glycemic load
 HR: adjusted for age, sex and stage, based on joint Cox proportional hazards models

* HRs significantly differed between cancer specific and other deaths ($p < 0.05$)