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Emily K. McCollum Date

RETROSPECTIVE COHORT STUDY OF INCIDENT RECTAL CANCER FOLLOWING RADIATION TREATMENT FOR PROSTATE CANCER

By

Emily K. McCollum
Master of Public Health

Epidemiology

_____

Michael Goodman, MD, MPH
Faculty Advisor

RETROSPECTIVE COHORT STUDY OF INCIDENT RECTAL CANCER FOLLOWING RADIATION TREATMENT FOR PROSTATE CANCER

By

Emily K. McCollum

B.S.
Clemson University
2005

Thesis Committee Chair: Michael Goodman, MD, MPH

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
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Abstract

RETROSPECTIVE COHORT STUDY OF INCIDENT RECTAL CANCER

FOLLOWING RADIATION TREATMENT FOR PROSTATE CANCER

By Emily K. McCollum

The association between prostate cancer radiation treatment and subsequent rectal cancer risk has not been well examined in the past. The current investigation seeks to add to the existing evidence by differentiating between the two major forms of radiation treatment used for prostate cancer, external beam radiation (EBRT) and brachytherapy. A cohort of men diagnosed with prostate cancer between 1995 and 2008 was obtained from the Surveillance Epidemiology and End Results database. Data was analyzed using a Cox proportional hazards model stratified by race and the results were expressed as adjusted hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs). Brachytherapy was associated with the largest increase in rectal cancer rates with HR (95% CIs) of 1.24 (1.22–1.26) for whites, 1.27 (1.20-1.34) for blacks, 1.29 (1.19-1.40) for Asians/Pacific Islanders and 1.17 (1.01-1.35) for persons whose race was unknown or not reported. There was no association between EBRT and rectal cancer incidence with HR estimates in the 0.94-1.03 range and all CIs including unity. The corresponding HRs for EBRT plus brachytherapy were also significantly elevated in almost all race categories (except for those patients whose race was unknown), but the magnitude of the association was lower than that for brachytherapy alone. The cause of this difference between the two main radiation treatments cannot be fully discerned without access to data on dosage and duration. If confirmed, these results should be used to inform patients and their physicians in making prostate cancer treatment decisions and in monitoring log-term treatment outcomes.

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BACKGROUND/LITERATURE REVIEW

Introduction

Prostate cancer is the most common malignancy among men in the United States, and is the second most common cause of cancer-related death after cancer of the lung and bronchus. It accounts for 28% of the incident cancer cases in men. Based on the data from 2002 to 2006, the United States incidence of prostate cancer was 155.5 per 100,000 men [1]. While cancer is typically thought of as an unusual event, prostate cancer is so common that it is almost expected for aging American men to be diagnosed with prostate cancer. It has been previously shown that a greater percentage of men over the age of 50 die with as opposed to from prostate cancer [2]. The American Cancer Society projects that in 2010 there were 217,730 new prostate cancer cases diagnosed and 32,050 men died of the disease [1].

Advances in early detection and treatment options have resulted in decreased prostate cancer death rates. In 2006, 28,372 men died as a result of prostate cancer compared to the 32,378 prostate cancer deaths recorded in 1990, a 38.9% decrease [1]. While survival following prostate cancer diagnosis differs by race and cancer stage, recent data indicate that the five-year survival for all stages and all races is nearly 100% [1].

Treatment Options

There is a wide range of treatment options available for prostate cancer. Currently there are four major treatment modalities: radical prostatectomy, brachytherapy (internal radiation therapy), external beam radiation therapy (EBRT), and androgen

deprivation therapy [3]. In addition, some patients choose watchful waiting in which the cancer is not immediately treated, but the patient is actively followed with regular prostate specific antigen (PSA) testing and follow up biopsies. These treatment choices may significantly impact the patient's quality of life and are associated with a variety of adverse effects depending on treatment and must be continually studied for long-term effects as a result of the increased survival of patients.

Recent studies indicate that overall 6.8% of prostate cancer patients elect watchful waiting as opposed to immediate treatment, 49.9% elect prostatectomy, 11.6% choose EBRT, 13.3% are treated with brachytherapy, 14.4% are treated with androgen deprivation therapy, and the remaining 4.0% are treated with newer treatments such as cryoablation, in which a probe is used to sections of the prostate thereby destroying cancerous tissue [3]. Time trends in treatment preference indicate that in the 1990s low risk patients tended to choose brachytherapy and androgen deprivation therapy as opposed to radical prostatectomy and watchful waiting. However, from 2000 to 2007 those trends have been steadily reversing, with 59.5% of low risk patients choosing radical prostatectomy, only 14.8% choosing brachytherapy, and 6.1% choosing EBRT. Alternatively, the use of radical prostatectomy among high risk patients has been rather stable since 1990, about 23%, while the amount of patients choosing EBRT has been decreasing recently (currently at 14.0%), as more patients opt for androgen deprivation therapy (45.5%) [3].

The Surveillance Epidemiology and End Results (SEER) registry data pertaining to prostate cancer patients indicate that among Caucasians 24% are treated with radical prostatectomy and 38.3% are treated with radiation therapy. The corresponding

percentages for radiation therapy and radical prostatectomy among African Americans are 39% and 16.9% respectively [4]. Other studies have confirmed that African American men tend to seek non-surgical treatments [5, 6].

Long-term effects of radiation therapy

The effect of radiation treatments on the development of subsequent cancers within the radiation field has been much debated in the past due to conflicting research. Because radiation exposure is a risk factor for many cancers, it stands to reason that exposure of organs to radiation during the process of cancer treatment could lead to subsequent cancers originating in those organs [7, 8].

A few studies have been conducted to investigate the possible association between treating a primary rectal cancer with radiation therapy and subsequent development of cancer in the prostate. One cohort study, found that among the rectal cancer patients treated with EBRT, there was a 72% reduction in prostate cancer diagnosis [9]. The authors theorized that unintentional irradiation of the prostate and/or testes in these patients may sterilize or reduce subclinical cases of prostate cancer, thereby reducing the incidence of prostate cancer in this patient subgroup [9]. A similar study examining the risk of prostate cancer following rectal cancer irradiation also found that a significant decrease in risk of prostate cancer [10].

The relation between radiation therapy for prostate cancer and subsequent cancers in other organs is conflicting. Some studies demonstrated that after controlling for confounders men who received radiation therapy for prostate cancer did not have an increased incidence of cancers in surrounding areas, such as the rectum and bladder, compared to patients who underwent other types of treatment [11, 12]. Conversely,

several studies have found an increased risk of developing cancer in areas within the radiation field [13-18]. One study found increased odds of subsequent cancer following EBRT that varied based on location; the odds ratios (OR) and the corresponding 95% confidence intervals (CIs) were 1.60 (95% CI 1.29-1.99) in the rectum, 1.63 (95% CI 1.44-1.84) in the bladder, and 1.85 (95% CI 1.30-2.63) in the transverse colon [13]. Another study found that prostate patients who received radiation therapy of any kind had a 15% increase in risk of subsequent cancer after 5 years and a 34% increase after 10 or more years [14]. A study that compared the EBRT and brachytherapy separately determined that at greater than 10 years of follow-up patients who received either EBRT alone or EBRT combined with brachytherapy were significantly more likely to have rectal cancer with hazard ratios (HRs) of 1.79 (95% CI 1.05-3.07) and 3.25, (95% CI 1.25-8.44) respectively, while patients receiving brachytherapy alone did not have a significantly increased risk of rectal cancer (HR = 1.13, 95% CI 0.15, 8.42) [18].

Current study objectives

The purpose of the current project is to examine the association between radiation therapy for prostate cancer and the occurrence of incident rectal cancer using population-based data from the Surveillance Epidemiology and End Results (SEER) program. Additionally, the study will assess the differences in risk associated with various radiation therapy modalities, specifically brachytherapy and EBRT, after controlling for confounders. The SEER database provides data on cancer diagnosis, treatment, and overall end results for a 33-year period between 1973 and 2007. With increased follow-up time following prostate cancer, this study will be able to allow for an adequate lag time necessary to ensure that the subsequent cancers are more likely to be radiation-

induced [15, 19]. The SEER registry covers approximately 26% of the US population and collects data on cancer incidence and survival in the United States. In addition, the registry compiles data on patient demographics, and cancer stage, grade, and treatments. This information will be used to identify prostate cancer patients and determine those that were subsequently diagnosed with rectal cancer.

METHODS

Incidence data were obtained from the U.S. National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program [20]. SEER is a publically available database and the patient data contained within is completely de-indentified, for this reason IRB approval was not needed for this study. The SEER database utilizes the International Classification of Diseases for Oncology, Third addition (ICD-O-3) for the coding of all primary malignant neoplasms [21]. The ICD-O-3 directs the coding for anatomic site and histological type of neoplasm. Descriptive analyses included data from 1995 - 2008 in order to allow for an accurate comparison between brachytherapy and EBRT. Registries that did not contribute data until later years were included beginning with the first year they contributed as a SEER registry.

The SEER database was searched to identify men diagnosed with prostate cancer (ICD-O-3 code C61.9) between 1995 and 2008. Subjects were included in this retrospective cohort study based on their main exposure status: having received EBRT, brachytherapy (termed radioactive implants in SEER), a combination of EBRT and brachytherapy, or no radiation treatment. The primary outcome of interest was development of secondary rectal cancer, including rectum (C20.9), rectosigmoid junction (C19.9), anus (C21.0), anal canal (C21.1) and anorectum (C21.8). In order to exclude

preexisting rectal tumors, the follow-up period was not started until 6 months after prostate cancer diagnosis.

Additional demographic and disease variables included age at prostate cancer diagnosis, year of prostate cancer diagnosis, race, prostate cancer stage, and prostate cancer grade. Age at prostate cancer diagnosis was ultimately categorized into two groups (<67 and ≥67) divided at the median. Race was categorized into four groups: white, black, Asian/Pacific Islander, and other. Subjects eligible for the study were limited to local/regional prostate cancer stage. Prostate cancer grade was categorized as grade I – II, grade III – IV, and unknown. Year of prostate cancer diagnosis was grouped roughly at 4 year intervals: 1995 – 1999, 2000 – 2004, and 2005 – 2008. Receipt of radiation treatment was categorized as none, external beam radiation therapy (EBRT), radioactive implants (brachytherapy), and combination of EBRT and implants.

Unadjusted Kaplan-Meier survival curves accompanied by the corresponding log-rank tests were used to compare rates of rectal cancer across different radiation treatment groups. Time to event was calculated as the number of years from prostate cancer diagnosis until subsequent diagnosis of rectal cancer, death, or end of follow-up using SEER*Stat (Surveillance Research Program, National Cancer Institute SEER*Stat software (www.seer.cancer.gov/seerstat) version 6.6.2). Multivariate analysis was conducted using Cox proportional hazard models controlling for the following factors: age at prostate cancer diagnosis, year of prostate cancer diagnosis, race, and prostate tumor grade.

Proportional hazard assumptions were assessed graphically using log(-log) survival curve comparisons. The results of the multivariate analysis are presented as

hazard ratios (HRs) with corresponding 95% confidence intervals (95% CIs). Possible collinearity and multicolinearity in the model was assessed using the collingenmod v9.c macro in SAS v 9.2 [22]. The model was examined for interaction between the radiation treatment variable and each of the covariates in the model. All statistical analyses were carried out using SEER*Stat or using SAS v9.2 software (SAS Institute Inc., Cary, NC).

RESULTS

A total of 208,016 men diagnosed with prostate cancer between 1995 and 2008 were enrolled in this retrospective cohort study. Within this cohort, 125,333 (60.25%) of the participants had no radiation treatment, 49,574 (23.8%) received EBRT, 19,575 (9.4%) had brachytherapy and 13,534 (6.5%) were treated with a combination of EBRT and brachytherapy. Table 1 shows the clinical and demographic characteristics of the cohort by radiation treatment group. Notably, a majority of the patients receiving EBRT or a combination therapy were 67 years or older (66.68% and 51.4% respectively) while the age distribution for patients having brachytherapy or no radiation was more even. Whites represented 81.64% of men in the no radiation group, 76.88% among those treated with EBRT, 84.66% among patients that received brachytherapy, and 77.28% in the combination (EBRT and brachytherapy) group. Blacks were the next most common racial group ranging from 9.61% for brachytherapy to 17.13% for the combination treatment. Grade I-II (well to moderately differentiated) prostate tumors made up 82% of the brachytherapy group but only 64.76% of the no radiation group, 61.56% of the EBRT group, and 59.54% of the combination treatment group. Among patients who developed a secondary cancer of interest, tumors in the rectosigmoid junction were most common in all treatment groups, followed by tumors of the rectum.

The Kaplan-Meier survival plots (using rectal cancer as the event of interest) for different radiation treatment categories are shown in Figure 1. The largest difference in survival was seen for those receiving brachytherapy compared to no radiation. EBRT patients experienced rectal cancer-free survival that was very similar to that in the no radiation treatment group. By contrast the age-adjusted survival curves (Figure 2) demonstrated that patients that received no radiation treatment had the lowest incidence rates of rectal cancer followed by EBRT, combination of EBRT and brachytherapy and brachytherapy alone.

The multivariate analyses demonstrated statistically significant interactions between race and radiation treatment and for this reason the final Cox proportional hazards model was stratified by race and adjusted for age, diagnosis year, and grade (Table 2). Brachytherapy was associated with the largest increase in rectal cancer rates with HR (95% CIs) of 1.24 (95% CI 1.22 – 1.26) for whites, 1.27 (1.20-1.34) for blacks, 1.29 (1.19-1.40) for Asians/Pacific Islanders and 1.17 (1.01-1.35) for persons whose race was unknown or not reported. There was no association between EBRT and rectal cancer incidence with HR estimates in the 0.94-1.03 range and all CIs including unity. The corresponding HRs for EBRT plus brachytherapy were also significantly elevated in almost all race categories (except for those patients whose race was unknown), but the magnitude of the association was lower than that for brachytherapy alone

DISCUSSION

As previously noted, currently available studies have been inconsistent in determining the association between prostate cancer radiation treatment and subsequent

rectal cancer development. Moreover many such studies have failed to differentiate between the various forms of radiation.

The majority of patients in our cohort, roughly 60%, did not receive radiation therapy; while EBRT was the favored radiation method (23.8%), followed by brachytherapy (9.4%). This distribution, as reported by SEER, does not exactly match the treatment trends discussed elsewhere [3]. However, the slight differences are likely due to the time span represented in the current cohort. Furthermore, as previously seen, it was found that white patients were more likely to receive brachytherapy compared to Blacks over EBRT whereas higher proportions of Black patients were treated with EBRT.

Our results indicate that brachytherapy patients were more likely to develop rectal cancer, compared to patients who received no radiation treatment. Patients treated with a combination of EBRT and brachytherapy also experienced an increase in rectal cancer but not as severe as in those receiving brachytherapy alone. By contrast there was no evidence that EBRT alone was associated with rectal cancer risk.

These results agree with previous findings of a small increased risk of subsequent rectal cancer for patients receiving brachytherapy [16]. A potential explanation for the differences in rectal cancer risk posed by EBRT and brachytherapy may be radiation dose and pattern of dose delivery. For example, EBRT can be directed at different angles to offer the most effective radiation dose to the prostate tumor. Altering the direction of the beam also affects the amount of surrounding tissue that is exposed to radiation in the process. The time course of treatment may also be a factor as EBRT is administered at

intermittent doses over a period of weeks whereas brachytherapy continues to expose the surrounding tissues to radiation at a more constant rate.

One of the main strengths of this study is the overall large sample size. The population-based nature of the SEER database allowed for multivariable and subgroup analysis that had not been conducted previously. Stratified analyses allowed for examination of the relation between prostate cancer treatment and subsequent risk of rectal cancer within each racial/ethnic group. To our knowledge this is the first analysis of this type. This study also had the longest follow-up of brachytherapy patients available to date.

Given the retrospective nature of this study, it may be subject to several limitations. While the SEER database has a reputation of containing high quality data some coding mistakes were likely present. Additionally, SEER does not provide data on the dose or duration of treatment for each patient, not does allow controlling for socioeconomic status, co-morbidities, family history, and other risk factors for rectal cancer as well as characteristics of health care providers that may affect quality of care and quality of follow up among prostate cancer patients. As treatment methods change the association between radiation and subsequent rectal cancer may also change over time.

CONCLUSIONS

Patients treated with brachytherapy only or with a combination of EBRT and brachytherapy experienced a small increase in subsequent rectal cancer. The results for patients treated with EBRT indicate that no evidence of increased rectal cancer risk. The increase in rectal cancer following brachytherapy also differed by race indicating that the

association was somewhat more pronounced in Blacks and Asian/Pacific Islanders than in whites. Future studies should examine additional factors such as radiation treatment characteristics such as dose and type, length of the interval between prostate cancer treatment and subsequent rectal cancer diagnosis, and different primary sites within the rectal cancer category. The current information, while not definitive, should be used to inform patients about their treatment options. Clinicians should also be aware of these findings in order to appropriately monitor and treat their patients.

TABLES

Table 1: Clinical and Demographic Characteristics by Radiation Treatment Type for Patients with Prostate cancer: SEER 1995-2008

Patient characteristics		**None (n=125,333)**		**EBRT (n=49,574)**		**Brachytherapy (n=19,575)**		**Combination: EBRT+ Brachy (n=13,534)**	
		Count	%	Count	%	Count	%	Count	%
Age at Diagnosis	<67	66,098	52.74	16,516	33.32	9,690	49.50	6,577	48.6
	67<	59,235	47.00	33,058	66.68	9,885	50.50	6,957	51.4
Race	White	102,320	81.64	38,112	76.88	16,572	84.66	10,459	77.28
	Black	14,540	11.60	7,107	14.34	1,881	9.61	2,318	17.13
	Asian or Pacific Islander	5,539	4.42	3,756	7.58	896	4.58	637	4.71
	Other/Unknown	2,934	2.34	599	1.21	226	1.15	120	0.88
Grade	Grade I - II	81,169	64.76	30,518	61.56	16,051	82.00	8,058	59.54
	Grade III - IV	39,583	31.58	18,167	36.65	3,090	15.79	5,255	38.83
	Unknown	4,581	3.66	889	1.79	434	2.22	221	1.63
Year of Diagnosis	1995-1999	43,017	34.32	17,880	36.07	3,612	18.45	3,966	29.30
	2000-2004	46,827	37.36	19,032	38.39	9,199	46.99	5,904	43.62
	2005-2008	35,489	28.32	12,662	25.54	6,764	34.55	3,664	27.07
Secondary Cancer	Rectum	96	0.08	55	0.11	14	0.07	11	0.08
	Rectosigmoid Junction	306	0.24	157	0.32	36	0.18	44	0.33
	Anus, Anal Canal, Anorectum	15	0.01	13	0.03	5	0.03	2	0.01
	No Rectal Cancer	124,916	99.67	49,349	99.55	19520	99.72	13477	99.58

Table 2: Cox Multivariate Survival Analysis of the Associations between Different Types of Radiation Treatment for Prostate Cancer and Subsequent Cancer of the Rectum or Rectosigmoid Junction Stratified by race; SEER –1995 - 2008

	White		Black		Asian/Pac. Isl.		Unknown	
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Radiation treatment								
None	ref		ref		ref		ref	
EBRT	0.96	0.95 - 0.98	0.98	0.95 - 1.01	0.94	0.90 - 0.99	1.03	0.93 - 1.13
Brachytherapy	1.24	1.22 - 1.26	1.27	1.20 - 1.34	1.29	1.19 - 1.40	1.17	1.01 - 1.35
EBRT + Brachytherapy	1.07	1.05 - 1.10	1.14	1.08 - 1.20	1.21	1.10 - 1.33	1.13	0.93 - 1.37

FIGURES

Figure 1: Kaplan-Meier Survival Plot by Radiation Treatment Modality

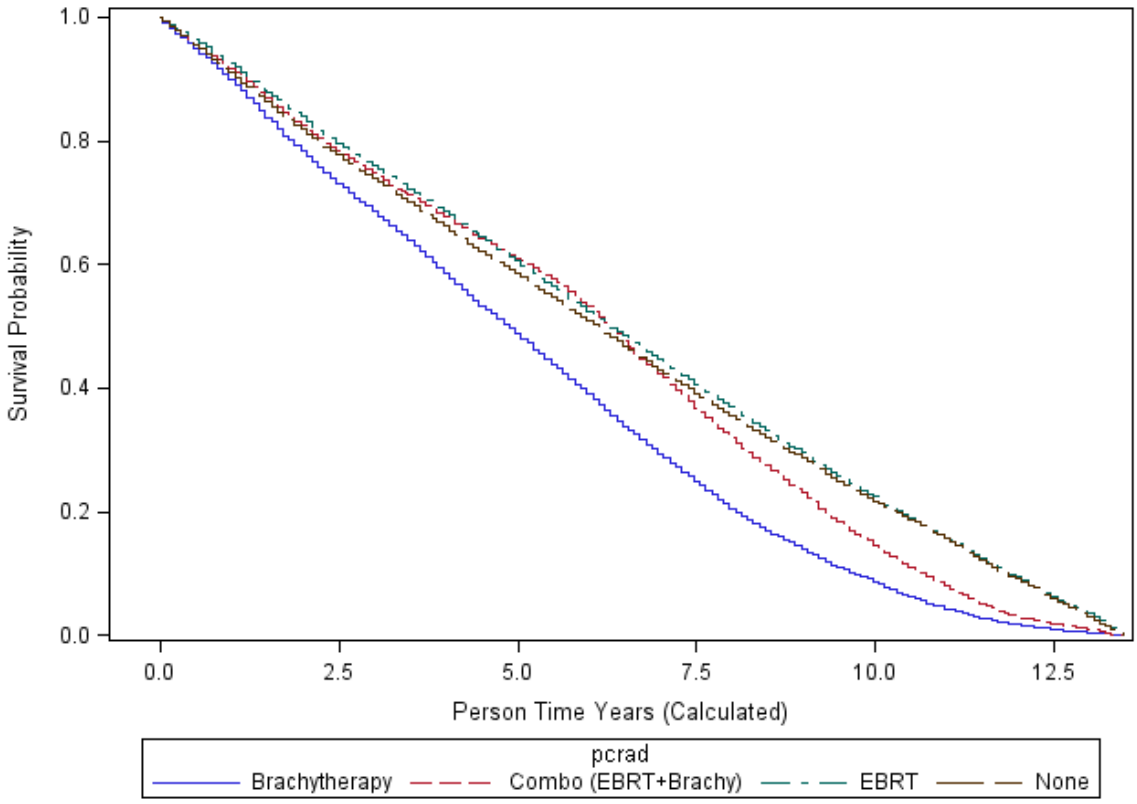
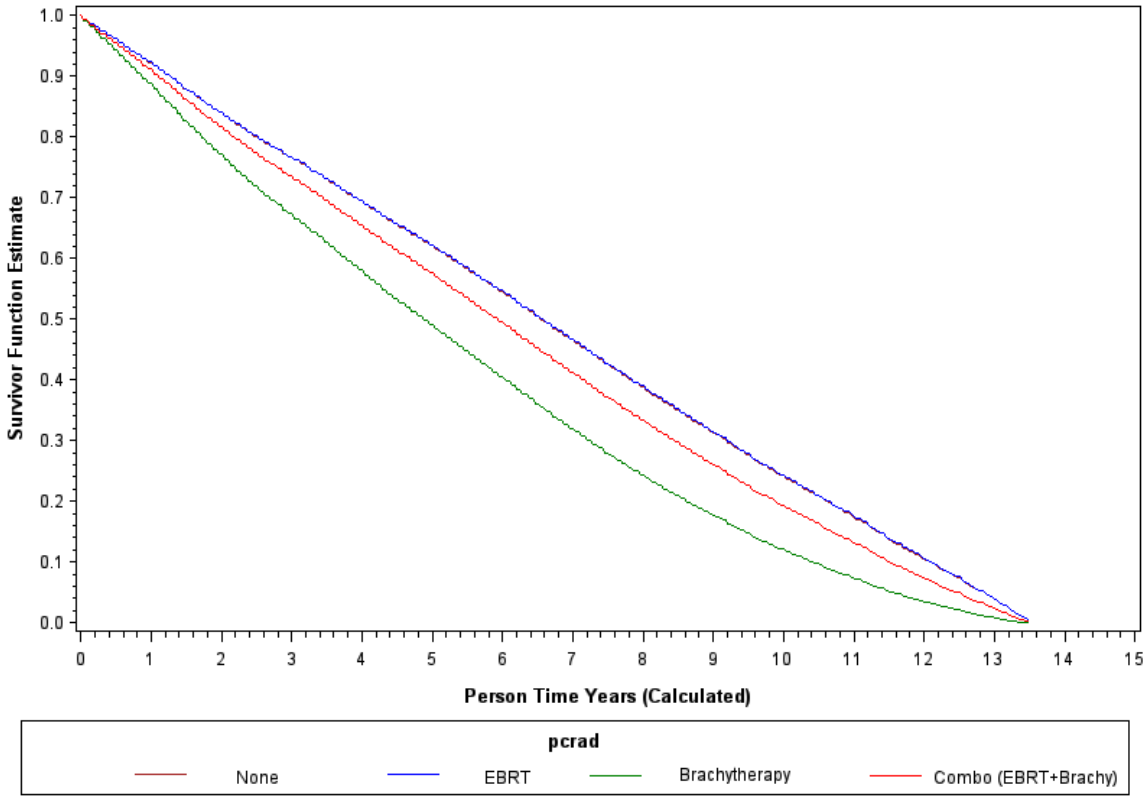


Figure 2: Survival Curve of Prostate Cancer Radiation Treatment Adjusted for Age



REFERENCES:

1. Jemal, A., et al., *Cancer statistics, 2010.* CA Cancer J Clin, 2010. **60**(5): p. 277-300.
2. Sanchez-Chapado, M., et al., *Prevalence of prostate cancer and prostatic intraepithelial neoplasia in Caucasian Mediterranean males: an autopsy study.* Prostate, 2003. **54**(3): p. 238-47.
3. Cooperberg, M.R., J.M. Broering, and P.R. Carroll, *Time trends and local variation in primary treatment of localized prostate cancer.* J Clin Oncol, 2010. **28**(7): p. 1117-23.
4. Du, X.L., et al., *Racial disparity and socioeconomic status in association with survival in older men with local/regional stage prostate carcinoma: findings from a large community-based cohort.* Cancer, 2006. **106**(6): p. 1276-85.
5. Schwartz, K., et al., *Interplay of race, socioeconomic status, and treatment on survival of patients with prostate cancer.* Urology, 2009. **74**(6): p. 1296-302.
6. Chu, D.I. and S.J. Freedland, *Prostate cancer. Socioeconomic status and disparities in treatment patterns.* Nat Rev Urol, 2010. **7**(9): p. 480-1.
7. Bostrom, P.J. and M.S. Soloway, *Secondary cancer after radiotherapy for prostate cancer: should we be more aware of the risk?* Eur Urol, 2007. **52**(4): p. 973-82.
8. Suit, H., et al., *Secondary carcinogenesis in patients treated with radiation: a review of data on radiation-induced cancers in human, non-human primate, canine and rodent subjects.* Radiat Res, 2007. **167**(1): p. 12-42.
9. Hoffman, K.E., et al., *External beam radiation treatment for rectal cancer is associated with a decrease in subsequent prostate cancer diagnosis.* Cancer, 2008. **112**(4): p. 943-9.
10. Huo, D., et al., *Association of colorectal cancer and prostate cancer and impact of radiation therapy.* Cancer Epidemiol Biomarkers Prev, 2009. **18**(7): p. 1979-85.
11. Kendal, W.S., et al., *Prostatic irradiation is not associated with any measurable increase in the risk of subsequent rectal cancer.* Int J Radiat Oncol Biol Phys, 2006. **65**(3): p. 661-8.
12. Pawlish, K.S., et al., *Risk of multiple primary cancers in prostate cancer patients in the Detroit metropolitan area: a retrospective cohort study.* Prostate, 1997. **33**(2): p. 75-86.
13. Moon, K., et al., *Cancer incidence after localized therapy for prostate cancer.* Cancer, 2006. **107**(5): p. 991-8.
14. Brenner, D.J., et al., *Second malignancies in prostate carcinoma patients after radiotherapy compared with surgery.* Cancer, 2000. **88**(2): p. 398-406.
15. Baxter, N.N., et al., *Increased risk of rectal cancer after prostate radiation: a population-based study.* Gastroenterology, 2005. **128**(4): p. 819-24.
16. Liauw, S.L., et al., *Second malignancies after prostate brachytherapy: incidence of bladder and colorectal cancers in patients with 15 years of potential follow-up.* Int J Radiat Oncol Biol Phys, 2006. **66**(3): p. 669-73.

17. Rapiti, E., et al., *Increased risk of colon cancer after external radiation therapy for prostate cancer.* Int J Cancer, 2008. **123**(5): p. 1141-5.
18. Nieder, A.M., M.P. Porter, and M.S. Soloway, *Radiation therapy for prostate cancer increases subsequent risk of bladder and rectal cancer: a population based cohort study.* J Urol, 2008. **180**(5): p. 2005-9; discussion 2009-10.
19. Jao, S.W., et al., *Colon and anorectal cancer after pelvic irradiation.* Dis Colon Rectum, 1987. **30**(12): p. 953-8.
20. *Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 9 Regs Research Data, Nov 2009 Sub (1973-2007) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2007 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2010, based on the November 2009 submission.*
21. Fritz, A.G., *International classification of diseases for oncology : ICD-O*. 3rd ed. 2000, Geneva: World Health Organization. vii, 240 p.
22. Davis, C., et al., *An example of dependencies among variables in a conditional logistic regression*, in *Modern Statistical Methods in Chronic Disease Epidemiology*, M. SH and P. RL, Editors. 1986, John Wiley and Sons, Inc: New York.

APPENDICES

APPENDIX I: SEER Data Use Agreement

Last Name: MCCOLLUM
SEER ID: 10124-Nov2010
Request Type: Internet Access

SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS PROGRAM
Data-Use Agreement for the 1973-2008 SEER Research Data File

It is of utmost importance to protect the identities of cancer patients. Every effort has been made to exclude identifying information on individual patients from the computer files. Certain demographic information - such as sex, race, etc. - has been included for research purposes. All research results must be presented or published in a manner that ensures that no individual can be identified. In addition, there must be no attempt either to identify individuals from any computer file or to link with a computer file containing patient identifiers.

In order for the Surveillance, Epidemiology, and End Results Program to provide access to its Research Data File to you, it is necessary that you agree to the following provisions.

1. I will not use - or permit others to use - the data in any way other than for statistical reporting and analysis for research purposes. I must notify the SEER Program if I discover that there has been any other use of the data.

2. I will not present or publish data in which an individual patient can be identified. I will not publish any information on an individual patient, including any information generated on an individual case by the case listing session of SEER*Stat. In addition, I will avoid publication of statistics for very small groups.

3. I will not attempt either to link - or permit others to link - the data with individually identified records in another database.

4. I will not attempt to learn the identity of any patient whose cancer data is contained in the supplied file(s).

5. If I inadvertently discover the identity of any patient, then (a) I will make no use of this knowledge, (b) I will notify the SEER Program of the incident, and (c) I will inform no one else of the discovered identity.

6. I will not either release - or permit others to release - the data - in full or in part - to any person except with the written approval of the SEER Program. In particular, all members of a research team who have access to the data must sign this data-use agreement.

7. I will use appropriate safeguards to prevent use or disclosure of the information other than as provided for by this data-use agreement. If accessing the data from a centralized location on a time sharing computer system or LAN with SEER*Stat or another statistical package, I will not share my logon name or password with any other individuals. I will also not allow any other individuals to use my computer account after I have logged on with my logon name and password.

8. For all software provided by the SEER Program, I will not copy it, distribute it, reverse engineer it, profit from its sale or use, or incorporate it in any other software system.

9. I will cite the source of information in all publications. The appropriate citation is associated with the data file used. (Please see either Suggested Citations on the SEER*Stat Help menu or the Readme.txt associated with the ASCII text version of the SEER data (CD #2).)

My signature indicates that I agree to comply with the above stated provisions.

Signature

4/14/2011

DATE Date

Please print, sign, and date the agreement. Send the form to The SEER Program:

- **By fax to 301-628-1295**
- **Or, e-mail a scanned form to seerfax@imsweb.com**

APPENDIX II: IRB exemption clarification, email correspondence

From: Dent, Donna
Subject: RE: Student Research Project
Date: August 21, 2010 11:03:24 PM EDT
To: emccoll@emory.edu

If you are analizing a public dataset then you do not need to submit to the IRB. It would not be "private identifiable data". If you are analizing non-identifiable data then you do not need to submit to the IRB. It also would not be "private identifiable data". See the list of Examples of Identifiers on the IRB website (http://www.irb.emory.edu/researchers/socio/socio.cfm). If the data has been de-identified then you would need to clarify who de-identified it? Are they engaged in the research? If they are then you will probably need to submit to the IRB.

From: Emily McCollum [emccoll@emory.edu]
Sent: Thursday, August 19, 2010 11:31 AM
To: Dent, Donna
Subject: Student Research Project

Hello Ms Dent,

I am a current student at the Rollins School of Public Health and am beginning to work on my thesis project. My faculty advisor suggested that I may not need IRB approval to continue with my project but suggested that I check to be sure.

The project that I have in mind will look at outcomes following treatment for prostate cancer and use data from the Surveillance Epidemiology and End Results (SEER) database. Given the nature of this publicly available database the data I would like to use are de-identified and previously collected as part of routine surveillance.

My question then is whether I need to submit for approval given the nature of the data, or if I can just proceed with my research project as though exempt because of the de-identified, publicly available, routine surveillance data that I would like to use.

I greatly appreciate any guidance you can provide on this matter.

Thank you.

Emily McCollum, emccoll@emory.edu
Master of Public Health Candidate, May 2011
Department of Epidemiology, Rollins School of Public Health, Emory University