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Does Radiation Treatment of Prostate Cancer Increase Risk for Rectal Cancer?

The Perfect Storm

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Background

Prostate Cancer is the leading reportable cancer diagnosed among U.S. men. An estimated **238,590** (20,430 in California) new cases are expected during 2013.

Approximately **1 in 6** U.S. men will have a prostate cancer diagnosis during his lifetime.

Background



THE
PERFECT STORM

Background

Phase 1 of *The Perfect Storm*

Wide-scale PSA-screening beginning in 1990, producing a remarkable change in stage at diagnosis for prostate cancer (PC), with the overwhelming majority of cases, today, diagnosed as organ confined (localized) disease that has excellent survival, regardless of treatment.

Background

Phase 2 of *The Storm*

Over time, there were increases in PSA screening among younger and younger men and a tendency to lower PSA cut-points used prognostically, in attempts to identify more aggressive cancers.

Phase 3 – The weather worsens

Adoption of *Gleason's score* produced higher grading (upward grade migration) for many PCs, contributing to a tendency for more aggressive treatment.

Problem: - The Storm Goes Unnoticed

5-year relative survival for PC was 68% in 1975-77, 88% in 1987-89, and today is the same as that measured among men not having PC; 100%.

Much of this “remarkable survival improvement” resulted from the increasing proportion of PC cases diagnosed at early-stage during more contemporary years.

Two clinical trials failed to identify significant differences in localized PC among men receiving prostatectomy, external beam radiation therapy, and active surveillance (watchful waiting).

Problem: Lessons From Past Storms

Supradiaphragmatic irradiation for treatment of Hodgkin's disease and x-ray therapy for postpartum mastitis are accepted contributing causes of breast cancer 5-25 years post treatment.

X-ray treatment of enlarged thymus during infancy is accepted as a contributing cause of thyroid cancer extending to 40 years post treatment.

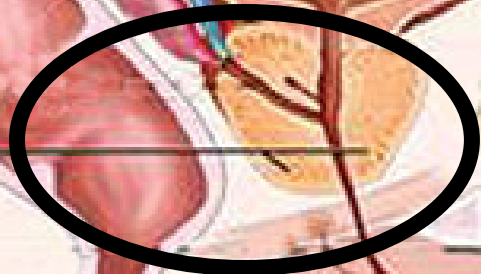
Previous studies of rectal cancer occurrence among prostate cancer cases treated with radiation produced mixed findings.

Problem: - The Storm Arrives

The proximity of the prostate gland and rectum ensures that cancer-directed radiation therapy for PC, necessarily exposes perirectal tissue to ionizing radiation.

Ureter
Lymph node
Rectum
Bladder
Prostate gland
Urethra

Seminal vesicle



Generalized Aim:

We sought to assess whether California men diagnosed with localized prostate cancer from 1988-2005, treated with radiation therapy (AnyRT), experienced higher rectal cancer risk (hazards) more than 5 through 23 (5+) years following PC treatment (1993-2010), relative to men treated with prostatectomy (SURG) not receiving AnyRT.

Specific Hypotheses include the following contrasts:

Model 1: AnyRT vs. SURG

Model 2: NoRT+NoSurg vs. SURG

Model 3: EBRT+BT vs. SURG
EBRT vs. SURG
BT vs. SURG

Methods:

Prostate Cancers (PC)
in California 1988-2005

351,684

Organ-confined
at Diagnosis

98,510

253,174

Completed >5 Years of rectal cancer free
follow-up (1993-2010) after PC DX

72,284

180,890

Treated with Radiation only,
Surgery Only,
No Radiation & No Surgery
(Excludes Mixed & Unknown Treatment)

22,373

158,517

Men Dxed with
Rectum or
Rectosigmoid jx
(Rectal) Cancer
1993-2010

55,724

Diagnosed with
Rectal Cancer
>5-years following PC
1993-2010

607

Univariate Findings:

Table 1. Counts, percentages, and univariate odds ratios (OR) for rectal cancer occurring greater than five-years following localized prostate cancer (PC) diagnosed from 1988-2005 that was treated using any radiation therapy (AnyRT), external beam radiation therapy (EBRT), or brachytherapy (BT), EBRT+BT, or did not receive radiation therapy or surgery (No RT+No SURG). Data from the California Cancer Registry.

TREATMENT	Rectal Cancer				Total	OR; 95% CI
	Yes		No			
	N	(Col%)	N	(Col%)		
AnyRT	249	41.0%	60,390	51.5%	60,639	1.07; 0.89-1.28
EBRT	201	33.1%	44,822	43.9%	45,023	1.16; 0.95-1.41
BT	26	4.3%	11,106	16.2%	11,132	0.61; 0.39-0.92
EBRT+BT	22	3.6%	4,462	7.2%	4,484	1.27; 0.80-2.01
No RT+No SURG	136	22.4%	40,122	41.1%	40,258	0.88; 0.71-1.09
SURG	<u>222</u>	36.6%	<u>57,398</u>	55.0%	<u>57,620</u>	1
Total	607	100.0%	157,910	100.0%	158,517	

Univariate Findings:

Table 1 Cont. Counts, percentages, and univariate odds ratios (OR) for rectal cancer occurring greater than five-years following localized prostate cancer (PC) diagnosed from 1988-2005 that was treated using radiation therapy (AnyRT), external beam radiation therapy (EBRT), brachytherapy (BT), EBRT+BT, did not receive radiation therapy or surgery (No RT+No SURG), or had missing treatment data, relative to prostatectomy (SURG). Data from the California Cancer Registry.

Covariates	Rectal Cancer				Total	OR; 95% CI
	Yes		No			
	N	Col(%)	N	(Col%)		
Age						
<50	5	0.8%	3,282	2.1%	3,287	0.34; 0.12-0.84
50-64	163	26.8%	51,766	33.0%	51,929	0.72; 0.59-0.87
65-74	300	50.1%	69,705	44.2%	70,005	1
75+	139	22.3%	33,157	20.8%	33,296	0.95; 0.77-1.16
Total	607	100.0%	157,910	100.0%	155,517	
Race/Ethnicity						
Asian-Other	32	5.3%	14,324	9.0%	14,356	0.55; 0.38-0.79
NH Black	49	8.1%	12,936	8.2%	12,985	0.95; 0.70-1.28
Hispanic	75	12.4%	17,329	11.0%	17,404	1.08; 0.84-1.39
NH White	451	74.3%	113,321	71.8%	113,772	1
Total	607	100.0%	157,910	100.0%	158,517	
Socioeconomic Status						
1 Lowest	66	11.5%	17,598	11.5%	17,598	1.03; 0.77-1.38
2	102	17.3%	25,578	16.5%	25,578	1.12; 0.88-1.44
3	128	21.0%	31,665	20.1%	31,665	1.13; 0.89-1.43
4	142	22.8%	36,852	23.1%	36,852	1.07; 0.85-1.34
5 Highest	169	27.4%	46,824	28.8%	46,824	1
Total	607	100.0%	157,910	100.0%	158,517	

Table 2. Model 1 - Proportional hazards ratios (HR) for rectal cancer (1993-2010, diagnosed more than five years following localized prostate cancer (PC) (1988-2005) that had been treated with Any RT relative SURG. Data from the California Cancer Registry.

Variable Categories	Hazard Ratio (HR)	95% CI for HR
Treatment		
AnyRT	1.44	1.18 - 1.75
SURG	1	

Age (4 categories)

Race/Ethnicity (4 categories)

Socioeconomic Status (5 categories)

Year PC Diagnosed (continuous variable)

Table 2. Model 2 - Proportional hazards ratios (HR) for rectal cancer (1993-20100, diagnose more than five years following diagnosis of localized prostate cancer (PC) (1988-2005) that had not been treated with AnyRT and not treated with SURG (NoRT+NoSURG). Data from the California Cancer Registry.

Variable Categories	Hazard Ratio (HR)	95% CI for HR
Treatment		
NoRT+NoSURG	1.13	0.88 - 1.46
SURG	1	

Age (4 categories)

Race/Ethnicity (4 categories)

Socioeconomic Status (5 categories)

Year PC Diagnosed (continuous variable)

Table 2. Model 3 - Proportional hazards ratios (HR) for rectal cancer (1993-20100, diagnose more than five years following diagnosis of localized prostate cancer (PC) (1988-2005) that had been treated EBRT+BT, EBRT Only or BT Only vs. SURG. Data from the California Cancer Registry.

Variable Categories	Hazard Ratio (HR)	95% CI for HR
Treatment		
EBRT+BT	1.60	1.03 - 2.49
EBRT Only	1.44	1.17 - 1.77
BT Only	1.29	0.85 - 1.97
SURG	1	

Trend p=0.0002

Age (4 categories)

Race/Ethnicity (4 categories)

Socioeconomic Status (5 categories)

Year PC Diagnosed (continuous variable)

Discussion/Conclusions:

These findings support hypotheses of increased rectal cancer hazards among localized PC cases treated with AnyRT, EBRT+BT, and EBRT modalities, relative to SURG.

Higher HRs for, **arguably**, higher radiation exposure modalities (EBRT+BT > EBRT > BT > SURG) support our contention that this temporal association may be direct.

Discussion/Conclusions:

This study did not evaluate benefits or other adverse effects associated with SURG, radiation therapy, other therapies, or active surveillance (NoRT+NoSURG) encountered in management of localized PC.

These findings should not be used as a solitary criterion for determination of treatment modality for localized PC and should be considered, together, with other benefits and harms encountered in prostate cancer treatment.

Limitations:

Beam radiation delivery modalities changed during the treatment-period (1988-2005) of our study, including a pattern of change from 3D conformal to IMRT and introduction of proton beam radiation therapy.

Reporting of these treatment modality differences is only available in CCR data after 2003, precluding study of the impact of these differences on rectal cancer hazards during most of our treatment-period.

We solicit ideas for how it might be possible to determine or impute beam radiation modality type used to treat individual prostate cancers for CCR cases treated during 1988-2003.

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Together, we are
“Winning the War on Cancer”

Thank You!