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Hematologic malignancies following external beam radiation therapy for localized prostate cancer

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The incidence of hematologic malignancies following external beam radiation therapy (EBRT) among prostate cancer patients has received limited attention despite evidence that radiation has a role in leukemogenesis and myelomagenesis. Therefore, we investigated the effect of external beam radiation therapy on acute myeloid leukemia and myeloma incidence among prostate cancer patients. We utilized the Surveillance, Epidemiology, and End Results database to identify a cohort of men (*n*=168,612) with newly diagnosed prostate adenocarcinoma between January 1988 and December 2003. Cox proportional hazard regression was used to estimate the hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) of acute myeloid leukemia and myeloma incidence following definitive therapy with EBRT alone, brachytherapy alone, or surgery alone compared to no definitive therapy. The cohort yielded 184 incident acute myeloid leukemia cases and 344 incident myeloma cases during 1,064,820 person-years of follow-up after prostate adenocarcinoma diagnosis. Patients treated with EBRT had a higher adjusted relative hazard of developing acute myeloid leukemia than patients treated with brachytherapy or surgery when each therapy group was compared to patients who were not

treated with definitive therapy (EBRT: HR=2.05, 95% CI 1.29, 3.26; brachytherapy: HR=1.22, 95% CI 0.46, 3.22; surgery: HR=1.24, 95% CI 0.77, 1.98). Patients treated with EBRT, brachytherapy, or surgery did not have increased adjusted relative hazards of developing myeloma when each therapy group was compared to patients who were not treated with definitive therapy (EBRT: HR=0.97, 95% CI: 0.70, 1.35; brachytherapy: HR=0.60, 95% CI: 0.28, 1.33; surgery: HR=1.02, 95% CI: 0.75, 1.39). Our findings suggest that acute myeloid leukemia incidence is a greater concern for patients treated with EBRT than brachytherapy for localized or locally advanced prostate adenocarcinoma. However, our results indicate that neither EBRT nor brachytherapy increases the relative hazard of myeloma incidence among patients with localized or locally advanced prostate adenocarcinoma. Ultimately, our findings may contribute to the collective evidence regarding the risks and benefits of external beam radiation therapy.

HEMATOLOGIC MALIGNANCIES FOLLOWING EXTERNAL BEAM RADIATION THERAPY FOR LOCALIZED PROSTATE CANCER

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HEMATOLOGIC MALIGNANCIES FOLLOWING EXTERNAL BEAM RADIATION THERAPY FOR LOCALIZED PROSTATE CANCER

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EBRT: external beam radiation therapy;

SDF-1: stromal cell-derived factor-1;

MMP-2: matrix metalloproteinase-2;

MMP-9: matrix metalloproteinase-9;

SIR: standardized incidence ratio;

CI: confidence interval;

SEER: Surveillance, Epidemiology, and End Results;

ICD-O-3: International Classification of Diseases for Oncology 3rd Edition

DAG: directed acyclic graph;

HR: hazard ratio;

NNT(harm): needed to treat (harm);

SD: standard deviation;

IQR: inter-quartile range;

AML: acute myeloid leukemia;

MGUS: monoclonal gammopathy of undetermined significance;

LHCs: lymphohematopoietic cancers;

Gy: Grays;

CHAPTER 1

BACKGROUND

Early diagnosis of prostate cancer because of prostate-specific antigen screening has resulted in an abundance of localized prostate cancer cases whose clinical significance remains undetermined over the lifetime of the patient.[1] A proportion of these patients may receive unnecessary treatments that have various adverse consequences. Conventional management of localized prostate cancer involves surgery, radiation therapy, or active surveillance.[2-5] Radiation therapy is predominantly administered in the form of external beam radiation therapy (EBRT) which entails high-dose localized delivery of ionizing radiation to the prostate. The immediate adverse consequences of surgery and radiation therapy for localized prostate cancer are well-documented.[4-6] However, the existing evidence regarding long-term adverse consequences of localized radiation therapy for prostate cancer patients is sparse and primarily limited to relative risk estimates for solid tumor incidence following EBRT.[7]

Limited information is available regarding acute myeloid leukemia and myeloma incidence following EBRT for localized prostate cancer despite evidence that ionizing radiation has a pronounced role in leukemogenesis and myelomagenesis.[8-10] The evidence regarding the effect of radiation on other hematologic malignancies is either unavailable (e.g. Waldenstrom's macroglobulinemia [11]) or increased relative risks have been observed for

atomic exposures but not therapeutic exposures (e.g. chronic myeloid leukemia[9,12]). This inconsistent effect of ionizing radiation on hematopoietic stem cells that give rise to hematologic malignancies is largely explained by differential cellular radiosensitivity.[8,9,13] We thus limited our investigation to acute myeloid leukemia and myeloma following EBRT to be consistent with the available evidence. Subsequently, the primary objectives of this dissertation were:

1. To systematically review the literature regarding the effect of EBRT on acute myeloid leukemia and myeloma incidence among prostate cancer patients.
2. To evaluate the effect of EBRT on acute myeloid leukemia incidence in a population-based cohort of patients with localized or locally advanced prostate adenocarcinoma.
3. To evaluate the effect of EBRT on myeloma incidence in a population-based cohort of patients with localized or locally advanced prostate adenocarcinoma.

CHAPTER 2

SYSTEMATIC REVIEW

Introduction

Early diagnosis of prostate cancer because of prostate-specific antigen screening has resulted in an abundance of localized prostate cancer cases whose clinical significance remains undetermined over the lifetime of the patient.[1] A proportion of these patients may receive unnecessary treatments that have various adverse consequences. The immediate adverse consequences of surgery and radiation therapy for localized prostate cancer are well-documented.[4-6] Furthermore, a recent systematic review[7] documented the existing evidence regarding long-term adverse consequences of localized radiation therapy for prostate cancer patients, but primarily focused on solid tumor incidence following EBRT. The evidence regarding incident acute myeloid leukemia and myeloma following EBRT among prostate cancer patients has not been synthesized despite the pronounced role of ionizing radiation in leukemogenesis and myelomagenesis.[8-10]

Acute myeloid leukemia is characterized by disrupted myeloid cell differentiation from hematopoietic stem cells[9,14,15] and myeloma is characterized by proliferation of clonal plasma cells from bone marrow-derived B cells.[9,16,17] Acute myeloid leukemia has a bimodal incidence distribution with peaks in childhood and late adulthood,[15] whereas myeloma is almost

exclusively a disorder of older adults[9.16.17]. Among adults, both malignancies are more common among males and Blacks for reasons currently unknown[9,14-17]. Acute myeloid leukemia and myeloma are also aggressive and incurable; the relative survival rates for both malignancies are low (5-year relative survival for individuals aged >50 years: acute myeloid leukemia=11.3%, myeloma=38.1%)[18].In contrast, the relative survival rate for localized or locally advanced prostate cancer is high (5-year relative survival=100%)[18], which illustrates the potentially detrimental impact on life expectancy for prostate cancer patients who develop acute myeloid leukemia or myeloma as a second malignancy.

Extensive chromosomal abnormalities, particularly chromosomal translocations and deletions, are common to the etiology of acute myeloid leukemia and myeloma.[9,14-17] Most of these chromosomal abnormalities are acquired (i.e. somatic as opposed to germinal) abnormalities induced by exogenous factors.[15] For example, acquired chromosomal abnormalities are found in 50% to 80% of acute myeloid leukemia patients and the prevalence of such abnormalities is particularly high among older adults and those with secondary acute myeloid leukemia.[15] These acquired chromosomal abnormalities are primarily the result of DNA double strand breaks caused by exogenous factors and subsequent errors in DNA repair mechanisms.[15]

EBRT is capable of inducing the DNA double strand breaks[19] that are hallmarks of leukemogenesis and myelomagenesis, particularly if areas with rich

sources of hematopoietic stem cells are exposed. Prostate cancer patients may be at risk of acute myeloid leukemia and myeloma following EBRT because of unintentional radiation exposure to the os coxae (pelvic bone), an area that contains the highest concentration of hematopoietic stem cells in adults and may be exposed to >50% of the dose from localized prostate irradiation.[20] EBRT also has the capacity to induce hematopoietic stem cell migration from other locations through a recruitment process mediated by stromal cell-derived factor-1 (SDF-1), matrix metalloproteinase-2, and matrix metalloproteinase-9 (MMP-2 and MMP-9) expression in irradiated tissue, which suggests that the exposure may not be limited to hematopoietic stem cells that populate the os coxae.[21] Ultimately, these direct and indirect processes may result in a substantial number of hematopoietic stem cells being exposed to the mutagenic effects of radiation, thereby increasing the malignant potential.[21]

A synthesis of the published literature could provide insight whether these biological mechanisms translate to clinical outcomes among prostate cancer patients. Furthermore, the synthesized evidence could contribute to the collective knowledge regarding the risks and benefits of EBRT among prostate cancer patients. Therefore, we performed a systematic review of the literature to critically evaluate the existing evidence regarding acute myeloid leukemia and myeloma incidence following EBRT among prostate cancer patients.

Methods

We searched peer-reviewed literature in PubMed/Medline to identify studies published in English between January 1970 and January 2010 that investigated acute myeloid leukemia or myeloma incidence following EBRT among prostate cancer patients. We used two search strategies to ensure that all eligible studies would be identified. The first strategy employed various combinations of the keywords radiation therapy, prostate cancer, second* malignancy (where * is a Boolean operator that searches permutations of the base word, e.g. secondary), and second primary malignancy to allow specificity in our search. The second strategy employed various combinations of the keywords acute myeloid leukemia, myeloma, multiple myeloma, and prostate cancer to allow sensitivity in our search.

The articles identified using each search strategy were merged into a collective database of potentially eligible studies. These potentially eligible studies were screened for eligibility. Systematic reviews, case reports, case series, editorials, and letters to the Editor which essentially functioned as reports of a case or case series were ineligible for critical review. However, reviews were used for backward citation tracking to search for any potentially eligible studies not previously identified. Only original studies that addressed EBRT and acute myeloid leukemia incidence or EBRT and myeloma incidence among prostate cancer patients were eligible for critical review. The evidence ascertained from critical reviews of eligible studies was described using narrative methods.

Results

Acute myeloid leukemia

Acute myeloid leukemia incidence following EBRT among prostate cancer patients was addressed in 4 previous studies[22-25]. Neugut et al. reported increased standardized incidence ratios (SIRs) for acute myeloid leukemia among patients treated with EBRT from 1973-1990 after follow-up periods of 6 months – <5 years (SIR=1.5, 95% confidence interval [CI]: 0.9, 2.3) and 5 years – 8 years (SIR=1.2, 95%CI: 0.4, 2.8) following prostate cancer diagnosis compared to the United States standard population.[25] Moon et al. also noted non-significantly elevated acute myeloid leukemia risk among prostate cancer patients treated with EBRT compared to patients who were not treated with EBRT,[24] whereas Brenner et al.[22] noted a decreased risk of acute myeloid leukemia among patients treated with EBRT compared to the United States standard population and Johnstone et al.[23] reported no statistically significant effect of EBRT on acute myeloid leukemia incidence when prostate cancer patients were compared to the Connecticut standard population. However, Moon et al.[24], Brenner et al.[22], and Johnstone et al.[23] did not provide point estimates and 95% CIs for the relative risk. Therefore, the magnitude and precision of the effect estimates from these analyses are unknown.

Myeloma

Myeloma incidence following EBRT among prostate cancer patients was addressed in two previous studies[22,23]. Brenner et al.[22] and Johnstone et al.[23] noted that EBRT does not increase the relative risk of myeloma among prostate cancer patients compared to the US standard population. However, point estimates and 95% CIs for the relative risk were not provided in either study. Therefore, the magnitude and precision of the effect estimates from these analyses are unknown. *Table 1* summarizes the results from studies pertaining to acute myeloid leukemia and myeloma following EBRT among prostate cancer patients.

Discussion

Our results indicate that published studies have primarily reported null results for acute myeloid leukemia or myeloma incidence following EBRT among prostate cancer patients. The collective evidence for these hematologic outcomes among prostate cancer patients may be further suggestive of null findings because we cannot exclude the possibility that additional studies with null results regarding these outcomes were never published (i.e. publication bias or publication bias *in situ*)[26]. However, the current evidence is based on 4 studies pertaining to acute myeloid leukemia incidence and two studies pertaining to myeloma incidence. Unfortunately, we identified only one study[25] that reported a relative risk estimate for acute myeloid leukemia incidence and no

studies identified in our review reported a relative risk estimate for myeloma incidence. Furthermore, the published studies regarding the effect of EBRT on acute myeloid leukemia and myeloma incidence are susceptible to key biases that preclude meaningful inferences.

Acute myeloid leukemia and myeloma are rare outcomes[9,14-17] that require large sample sizes to be adequately powered to detect potential therapy-related effects. The sample size (*n*=164) used in the study by Johnstone et al.[23] is severely underpowered for detecting an effect of EBRT on acute myeloid leukemia or myeloma incidence among prostate cancer patients, which raises the potential for type II error (β error)[27$^{p.153}$] (i.e. inappropriate conclusion that EBRT does not have a significant effect) and may explain the null results for both outcomes in the study.

Studies with adequate sample sizes to detect an effect for either outcome were hindered by the use of inappropriate comparison groups to estimate the relative risk. Nearly all of the studies[22,23,25] estimated SIRs for acute myeloid leukemia or myeloma incidence following EBRT by standardizing the age distribution of the prostate cancer cohort to the age distribution of the standard population (United States general population[22,25] or Connecticut general population[23]). The corresponding incidence rates of acute myeloid leukemia or myeloma for the standard population were subsequently used to generate an observed/expected ratio for each malignancy within the cohort. Such comparisons to the general population are inappropriate in the context of

investigating potential treatment-related effects because the general population does not represent a cohort with prostate cancer for whom EBRT could be administered (i.e. an inappropriate counterfactual contrast[27[p.54-55], 28[p.137-138]-30]). The inappropriate comparison group renders the estimates unsuitable for causal inference.[27[p.54-55], 28[p.137-138]-30] Additionally, factors other than age contribute to disparate baseline risk of acute myeloid leukemia and myeloma between patients with prostate cancer and the external population. Consequently, residual confounding would threaten validity even if the general population were an appropriate comparison group.[27[p.69]]

Studies that noted acute myeloid leukemia or myeloma incidence following EBRT among prostate cancer patients were also susceptible to residual confounding because of unaddressed confounding by indication (specifically confounding by severity and confounding by comorbidity), which can be particularly detrimental to observational studies of treatment effects.[31] Essentially, factors such as tumor grade guide treatment selection.[3] The use of clinical characteristics to select treatments may dramatically alter the distribution of such characteristics between the treatment groups and result in unequal baseline risks of acute myeloid leukemia or myeloma incidence. Therefore, failure to address characteristics that guide treatment selection in the analysis may yield biased results.

The studies identified in our review[22-25] included patients with all stages of prostate cancer in the analyses. A combined study population that includes

localized and metastatic cases may obscure interpretations regarding the effect of EBRT on acute myeloid leukemia and myeloma incidence. EBRT for localized prostate cancer is administered to the prostate with potential unintended radiation exposure to the pelvic region surrounding the prostate,[20] whereas EBRT for metastatic prostate cancer is administered for site-specific palliation[32] with potential unintended radiation exposure to various anatomic locations (bone or soft tissue) and thus involves various concentrations of cell populations at-risk of malignant transformation. A study population restricted to prostate cancer patients without distant metastasis increases the likelihood that EBRT targeted the prostate, which subsequently improves interpretation regarding the effect of EBRT on these hematologic malignancies because all patients would have received radiation to a similar anatomic location.

In summary, our results indicate that published studies have primarily reported null results for acute myeloid leukemia or myeloma incidence following EBRT among prostate cancer patients. However, our critical review of these published studies indicates a paucity of studies that are meaningful for clinical inference regarding acute myeloid leukemia and myeloma incidence following EBRT among prostate cancer patients. Valid evidence regarding acute myeloid leukemia and myeloma incidence following EBRT among prostate cancer patients is necessary given the biological plausibility of radiation-induced leukemogenesis and myelomagenesis. Such evidence could add significant

information regarding the potential long-term consequences of EBRT and thus facilitate informed treatment decisions for prostate cancer patients.

Table 1. Summary of studies that discussed acute myeloid leukemia or myeloma following external beam radiation therapy among prostate cancer patients.

Authors	Study period	Sample size (*n*)	Outcome(s)	Comparison Group	Results
Brenner et al. [22]	1973-1993	122,123	Acute myeloid leukemia; myeloma	Surgery (after standardizing both comparison groups to the United States population)	Individual estimates were not reported for acute myeloid leukemia or myeloma, but the authors noted that a statistically significant effect was not observed for either malignancy.
Johnstone et al. [23]	1974-1987	164	Acute myeloid leukemia; myeloma	Connecticut standard population	No estimates reported; only p-values indicated no differences in the incidence of acute myeloid leukemia or myeloma.
Moon et al. [24]	1973-1999	140,767	Acute myeloid leukemia	No EBRT (surgery + no definitive therapy)	No estimates reported; only indicated in discussion that a statistically non-significant increase in acute myeloid leukemia incidence was observed.
Neugut et al. [25]	1973-1990	141,761	Acute myeloid leukemia	United States standard population	6 months – <5 years: SIR=1.5 (95%CI: 0.9, 2.3) 5 years – 8 years: SIR=1.2 (95%CI: 0.4, 2.8) >8 years: SIR=0.4 (95%CI: 0.0, 2.0)

SIR: standardized incidence ratio

CHAPTER 3

ACUTE MYELOID LEUKEMIA

Introduction

Acute myeloid leukemia is the most common hematologic consequence of radiation therapy; this disorder is characterized by loss of hematopoietic function and rapid mortality, particularly as a second malignancy.[33,34] An increased relative risk of acute myeloid leukemia following localized radiation therapy has been reported for patients with primary breast or cervical cancer.[35,36] Prostate cancer patients may also be at risk of acute myeloid leukemia following localized radiation therapy because of unintentional radiation exposure to the os coxae (pelvic bone), an area that contains the highest concentration of hematopoietic stem cells in adults and may be exposed to >50% of the dose from localized prostate irradiation.[20] This unintentional exposure may result in a substantial number of hematopoietic stem cells being exposed to the mutagenic effects of radiation.

Previous investigations of acute myeloid leukemia incidence following radiation therapy among prostate cancer patients were hindered by underpowered analyses because of small sample sizes[7] and/or confounding by indication, a bias common to observational studies of treatment effect that may lead to inappropriate conclusions[31]. Furthermore, previous studies have included acute myeloid leukemia as one of multiple outcomes being investigated,

which raises the potential for spurious associations.[37] Therefore, we investigated the effect of definitive therapy with radiation therapy (external beam radiation therapy [EBRT] or brachytherapy) on acute myeloid leukemia incidence in a population-based cohort of 168,612 patients with localized or locally advanced prostate adenocarcinoma.

Methods

Study population

We queried the Surveillance, Epidemiology, and End Results 9 (SEER 9) database[38] to identify a cohort of patients with newly diagnosed localized or locally advanced prostate cancer. Men diagnosed between January 1988 and December 2003, with additional follow-up through December 2004, who were treated with EBRT, brachytherapy, surgery, or no definitive therapy and survived >1 year after prostate cancer diagnosis were eligible for inclusion in our analyses; patients with distant metastases at diagnosis were thus excluded. Prostate cancer was biopsy-confirmed in all but ~1% of patients who were diagnosed by alternate methods such as evaluation of prostate-specific antigen, clinical characteristics, or radiographic imaging because of potential biopsy-related adverse events among the very elderly. We used data between 1988 and 2003 because prostate cancer coding schemes were uniform in SEER 9 throughout this period,[39] which supports consistent classification of relevant variables and reduces the potential for period effects.[27$^{p.608}$]

Eligible patients with localized or locally advanced prostate adenocarcinoma were identified according to the SEER historic stage designation which classifies stage for prostate cancer patients as ‘local/regional’ or ‘distant’ and allows consistent definitions of stage over time.[39] Eligible patients with prostate adenocarcinoma were identified according to the International Classification of Diseases for Oncology 3rd Edition (ICD-O-3) histology code 8140.[40] Patients with histologic subtypes other than prostate adenocarcinoma were excluded to reduce potential confounding by indication because other histologic subtypes may require adjuvant chemotherapy that potentially increases the risk of acute myeloid leukemia and utilize different criteria for guiding treatment decisions, which could not be addressed using SEER data.[41-44]

Variables

We used the comprehensive SEER 9 database definition of acute myeloid leukemia which includes all French-American-British sub-classifications.[45] A categorical variable for therapy that consisted of mutually exclusive categories for the form of definitive therapy received (EBRT alone, brachytherapy alone, surgery alone, or no definitive therapy [i.e. no EBRT, brachytherapy, or surgery)] [reference category] was created using information from corresponding variables in the SEER 9 database. The database included a variable that specifically coded for initial therapy with EBRT or brachytherapy. A separate variable in the

database included a category that identified patients treated with cancer-directed surgery.

Data analysis

A minimal sufficient set of covariates for which to adjust in the analyses were identified using a directed acyclic graph (DAG)[46-48] which encoded risk factors for acute myeloid leukemia and clinical characteristics that guide treatment decisions for localized or locally advanced prostate adenocarcinoma[3,49-58]. We incorporated risk factors for de novo acute myeloid leukemia into the DAG because these factors may also be relevant to secondary acute myeloid leukemia when considered in the context of sufficient component causes.[27$^{p.6-18}$] Although certain chemotherapeutic agents are known to cause secondary acute myeloid leukemia,[33,34] such agents were irrelevant to our DAG because they are not conventionally used for patients with localized or locally advanced prostate adenocarcinoma.[3,53] Our DAG indicated that conditioning on age at prostate cancer diagnosis, ethnicity, prostate cancer grade, and comorbidity encouraged d-separation[46-48] between radiation therapy and acute myeloid leukemia incidence among patients with localized or locally advanced prostate adenocarcinoma. Consequently, we were able to estimate the effect of radiation therapy on acute myeloid leukemia incidence after adjusting for these covariates in a multivariable Cox proportional hazard model.

Age at diagnosis was included as a continuous covariate in our analyses. The patient's ethnicity was categorized as White (reference category), Black, or Other. Prostate cancer grade was categorized according to the American Joint Classification on Cancer guidelines for grading tumors (Grade I: Well-differentiated [reference category]; Grade II: Moderately differentiated, Grade III: Poorly differentiated; Grade IV: Undifferentiated).[59] Comorbidity was defined as physician-determined presence of comorbidity at the time of diagnosis that precluded surgery as a therapeutic option.

Descriptive statistics for baseline and follow-up characteristics were evaluated by treatment group. Cox proportional hazard regression with censored observations was used to estimate the hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) of acute myeloid leukemia incidence following definitive therapy with EBRT alone, brachytherapy alone, or surgery alone compared to no definitive therapy after adjusting for age at diagnosis, ethnicity, grade, and comorbidity. Person-time was measured in years from the date of prostate cancer diagnosis. Patients who did not develop acute myeloid leukemia were censored at the time of last follow-up, incident malignancy other than acute myeloid leukemia, or death. The proportionality assumption was evaluated by graphing and examining interaction terms in the model; no violations were detected. Furthermore, we estimated the number of patients with localized or locally advanced prostate adenocarcinoma needed to treat (harm) [NNT(harm)] with EBRT or brachytherapy for one case of acute myeloid leukemia to develop

during 5-year intervals of follow-up by estimating absolute risks from multivariable adjusted survival models of time to event outcomes.[60] We performed complete subject analyses[27[p.219]] because of the small proportion of eligible patients with missing values for relevant covariates.

Results

SEER 9 contained data for 177,023 men eligible for our analysis, but 8,411 (4.8%) men were excluded because of missing values for relevant covariates. Our study population thus consisted of 168,612 men. Patients who were not treated with definitive therapy were older (n=32,336; mean age=73.4, SD=9.0) than patients treated with EBRT (n=41,986; mean age=70.6, SD=7.0), brachytherapy (n=10,259; mean age=66.7, SD=7.8), or surgery (n=84,031; mean age=65.7, SD=9.1). The brachytherapy group had the lowest proportion of Blacks (brachytherapy=8.7%, surgery=9.6%, EBRT=12.1%, no definitive therapy=12.3%) and the lowest proportion of high grade tumors (poorly differentiated or undifferentiated) at diagnosis compared to the other treatment groups (brachytherapy=7.1%, surgery=18.4%, EBRT=21.4%, no definitive therapy=23.5%). Surgery was not recommended because of pre-existing comorbidity for 1,982 patients (1.2%), of whom 63.0% were treated with EBRT, 4.4% were treated with brachytherapy, and 32.6% were not treated with definitive therapy.

The cohort yielded 184 incident acute myeloid leukemia cases during 1,064,820 person-years of follow-up after prostate adenocarcinoma diagnosis. The EBRT group had the highest crude incidence density of acute myeloid leukemia during follow-up compared to the other treatment groups (EBRT=28/100,000 person-years, no definitive therapy=15/100,000 person-years, surgery=14/100,000 person-years, brachytherapy=11/100,000 person-years). The brachytherapy group accrued the shortest duration of follow-up (median=3.8 years, inter-quartile range [IQR]=2.4, 5.7) compared to other treatment groups, whereas the surgery group accrued the longest duration of follow-up (median=6.6 years, IQR=3.6, 10.2). The highest proportionate mortality during follow-up was observed in the no definitive therapy group compared to the other treatment groups (no definitive therapy=33.6%, EBRT=26.0%, surgery=21.5%, brachytherapy=5.8%). *Table 2* provides detailed demographic, clinical, and follow-up characteristics for the study population by treatment group.

The unadjusted relative risk of developing acute myeloid leukemia following definitive therapy with EBRT alone indicated a positive relation, whereas the unadjusted relative risk of acute myeloid leukemia following brachytherapy alone or surgery alone indicated an inverse relation (EBRT: HR=1.74, 95% CI 1.10, 2.74; brachytherapy: HR=0.80, 95% CI 0.31, 2.10; surgery: HR=0.82, 95% CI 0.52, 1.29). A higher relative risk of developing acute myeloid leukemia following definitive therapy with EBRT alone persisted after

adjusting for age at diagnosis, ethnicity, grade, and comorbidity (EBRT: HR=2.05, 95% CI 1.29, 3.26; brachytherapy: HR=1.22, 95% CI 0.46, 3.22; surgery: HR=1.24, 95% CI 0.77, 1.98). Correspondingly, the number of patients with localized or locally advanced prostate adenocarcinoma needed to treat (harm) with EBRT alone for one case of acute myeloid leukemia to develop was lower than the number needed to treat (harm) with brachytherapy alone at each 5-year interval of follow-up (EBRT: 5-year: NNT[harm]=1505; 10-year: NNT[harm]=527; 15-year: NNT[harm]=333; brachytherapy: 5-year: NNT[harm]=3433; 10-year: NNT[harm]=1198; 15-year: insufficient data). *Table 3* details the hazard ratios and corresponding 95% CIs from the unadjusted and adjusted models and *Table 4* details the number needed to treat (harm) for EBRT alone and brachytherapy alone for each 5-year interval.

Discussion

Our analysis of a population-based cohort of 168,612 men with localized or locally advanced prostate adenocarcinoma indicates that the relative risk of developing acute myeloid leukemia following definitive therapy with EBRT is 105% greater than no definitive therapy, but the relative risk of acute myeloid leukemia following brachytherapy is 83% lower than EBRT. We translated the relative risks of acute myeloid leukemia following EBRT and brachytherapy into absolute risks to provide further insight regarding the clinical relevance of our findings. Our results indicate that the number needed to treat with EBRT for one

case of acute myeloid leukemia to develop rapidly declines with increasing duration of follow-up (i.e. the absolute risk of acute myeloid leukemia following EBRT increases over time). However, our results also indicate that brachytherapy required more than twice as many treated patients for one case of acute myeloid leukemia to develop at each 5-year interval than EBRT and thus brachytherapy may be a suitable therapeutic alternative to EBRT for select patients in the context of acute myeloid leukemia risk.

Few studies with large samples of prostate cancer patients have discussed the effect of EBRT on acute myeloid leukemia incidence[22,24,25,61]; two of these studies[22,24] did not report relative risk estimates and none reported actuarial absolute risks. The two studies that reported relative risk estimates indicated a 50%[25] and a 22%[61] increased risk of acute myeloid leukemia following EBRT among prostate cancer patients. Our findings for EBRT are directionally consistent with these studies, but indicate a greater magnitude of effect. However, previous studies did not address confounding by indication,[31] which may explain the discrepant magnitude of effect. Confounding by indication should be addressed because certain prognostic characteristics are used to guide treatment decisions for localized prostate cancer, which may result in disproportionate distributions of these characteristics between treatment groups. The baseline risk of acute myeloid leukemia may be unequal between treatment groups if such characteristics are directly or indirectly (through mediated pathways) related to acute myeloid leukemia risk.

Characteristics that guide treatment decisions for localized prostate adenocarcinoma have been explicitly acknowledged[3] and were integrated into our DAG to identify confounding by indication[62]. Although DAGs are ultimately limited by the current state of knowledge, DAGs can facilitate in specifying a model that promotes comparability between treatment groups.[46-48,62] Consequently, effect estimates derived from our analyses could be meaningful for clinical inference.

Our finding regarding a lower magnitude of effect of brachytherapy compared to EBRT on acute myeloid leukemia incidence is consistent with several large-scale studies[24,63,64] that reported similar results among prostate cancer patients, albeit for malignant outcomes other than acute myeloid leukemia. The lower potential for unintentional radiation to adjacent structures following brachytherapy[65] may explain the lower magnitude of effect on acute myeloid leukemia incidence. Our results regarding brachytherapy are encouraging for both patients and providers who could develop concerns about the potential effects of radiation therapy on acute myeloid leukemia incidence. However, we urge conservative interpretation of our findings regarding brachytherapy because the median duration of follow-up for brachytherapy-treated patients is considerably shorter than for patients treated with other modalities. Brachytherapy was not commonly utilized in our cohort until 2000, which leaves the possibility that more acute myeloid leukemia cases could be revealed with extended follow-up. Additional follow-up data are necessary to

confirm the comparatively lower effect of brachytherapy on acute myeloid leukemia incidence observed in our analysis.

Other limitations of our study should also be considered for appropriate interpretation of our findings. This study was specifically designed to investigate the effect of radiation therapy with EBRT or brachytherapy on acute myeloid leukemia incidence. Other forms of radiation therapy, such as proton-beam radiation therapy, may have different effects on acute myeloid leukemia incidence because these procedures can deliver high-dose radiation with a lower potential for unintentional radiation to surrounding structures.[66] Future studies are necessary to elucidate whether the lower potential for unintentional radiation using other forms of radiation therapy results in a lower risk of acute myeloid leukemia.

Our analysis was limited by a lack of data regarding second-line therapy in the SEER database. A subset of patients treated with definitive therapy for localized prostate cancer have localized biochemical recurrence (defined as rising prostate-specific antigen following initial therapy) which could require salvage therapy.[67] Patients initially treated with surgery who have localized biochemical recurrence may be treated with salvage EBRT,[68] whereas patients initially treated with EBRT who have localized biochemical recurrence may be treated with salvage surgery or salvage brachytherapy[69]. However, the use of salvage therapy would affect the *interpretation* and not the *validity* of our effect estimates because salvage therapy would function as an intermediate (which

should not be adjusted)[70] and not a confounder in our analysis. Specifically, a confounder would need to be a common cause of initial therapy and acute myeloid leukemia (i.e. an ancestor of the exposure and outcome),[46-48,62] but salvage therapy would have been administered subsequent to initial therapy and thus cannot be a common cause. Mediation is a potential consideration for a limited scenario within our study. For example, if EBRT is related to acute myeloid leukemia incidence, then salvage EBRT for patients who were initially treated with surgery may explain the modest increase in relative risk of acute myeloid leukemia for the surgery group because the direct effect of surgery on acute myeloid leukemia incidence should be null based on biological improbability. Our effect estimate would thus indicate the total causal effect (i.e. combined direct and indirect effects)[71] of surgery on acute myeloid leukemia incidence. In contrast, salvage surgery for patients who were initially treated with EBRT is not a plausible explanation for the increased relative risk of acute myeloid leukemia following EBRT. Furthermore, salvage brachytherapy would have limited impact on acute myeloid leukemia incidence in the context of a linear no-threshold model of carcinogenesis[72] because of prior EBRT exposure.

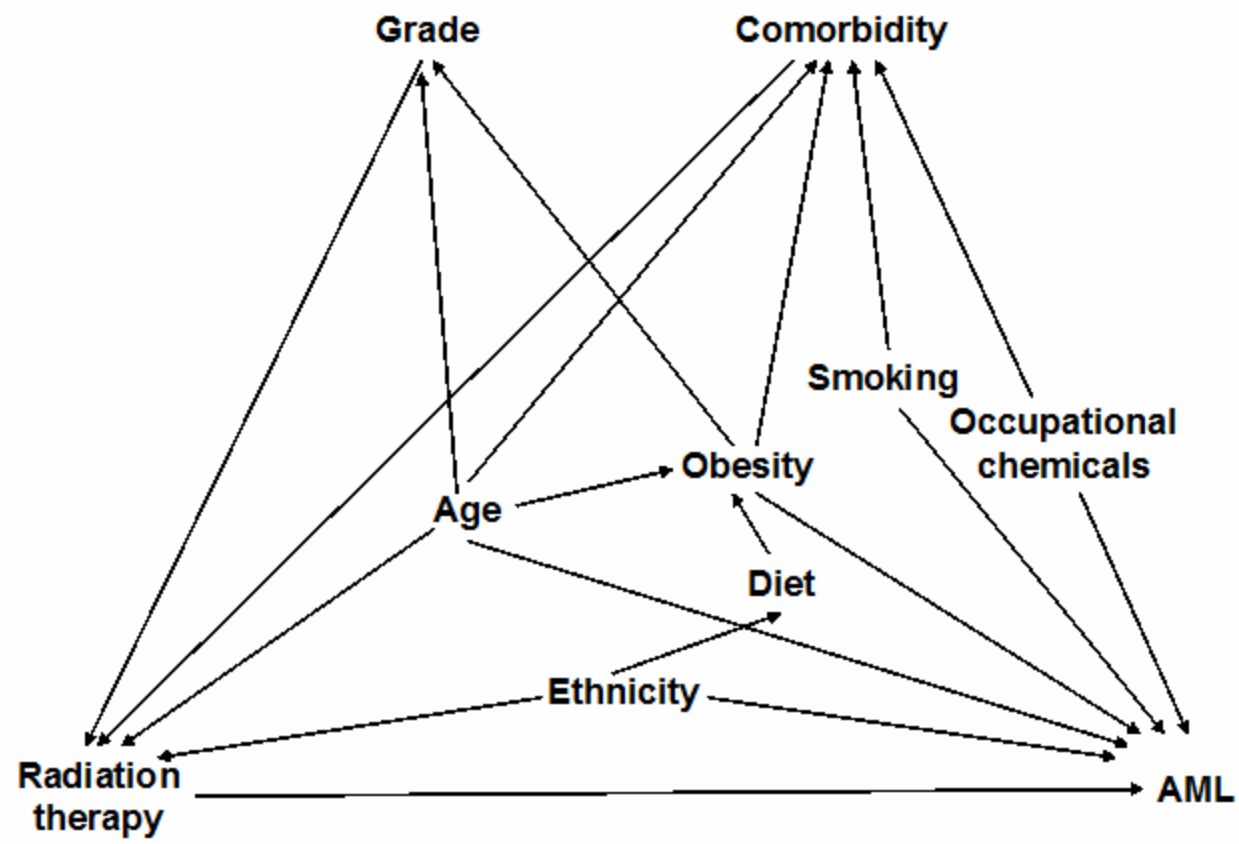
Some prostate cancer patients may have metastatic recurrence that is most often treated with cytotoxic chemotherapy.[73] Mitoxantrone, a topoisomerase II inhibitor, was the conventional first-line chemotherapy for metastatic prostate cancer until recently.[73] Topoisomerase II inhibitors are

known to induce acute myeloid leukemia,[33,34] which raises the possibility of mitoxantrone-related acute myeloid leukemia incidence in our study. However, no cases of mitoxantrone-related acute myeloid leukemia were documented in the literature until 2008,[74] which effectively excludes our study period. Nevertheless, if mitoxantrone-related acute myeloid leukemia were a possibility then chemotherapy would also function as an intermediate and not a confounder in our analysis. Therefore, if mitoxantrone-related acute myeloid leukemia were an unrecognized adverse event during our study period, our effect estimates would be indicative of the total causal effect (i.e. combined direct and indirect effects)[71] of EBRT on acute myeloid leukemia incidence among patients with localized or locally advanced prostate adenocarcinoma. Future studies with data regarding second-line therapy would be necessary to elucidate the direct and indirect effects of radiation therapy.

In summary, acute myeloid leukemia following radiation therapy is not a traditionally recognized adverse consequence for prostate cancer patients. Our study was designed to estimate the effect of radiation therapy on acute myeloid leukemia incidence among patients with localized or locally advanced prostate adenocarcinoma. Our analysis of a population-based cohort of 168,612 men with localized or locally advanced prostate adenocarcinoma indicates that the relative risk of developing acute myeloid leukemia following definitive therapy with EBRT is 105% greater than no definitive therapy, but the relative risk of acute myeloid leukemia following brachytherapy is 83% lower than EBRT. Furthermore, the

absolute effect of EBRT on acute myeloid leukemia incidence is more than 2-fold greater than brachytherapy. Our findings are useful for promoting recognition that acute myeloid leukemia may be an adverse consequence that is relevant to patients treated with EBRT for localized or locally advanced prostate adenocarcinoma.

Figure 1. Directed acyclic graph of the proposed causal structure for the relation between radiation therapy and acute myeloid leukemia (AML) among patients with localized or locally advanced prostate adenocarcinoma.



Note: This figure illustrates that age, ethnicity, grade, and comorbidity constitute a minimal sufficient set of covariates for which to adjust in the analysis because these covariates allow d-separation[46-48] of radiation therapy and AML among patients with localized or locally advanced prostate adenocarcinoma.

Table 2. Characteristics of patients with localized or locally advanced prostate adenocarcinoma in the Surveillance, Epidemiology, and End Results database; 1988-2003.

Variable	**External beam radiation therapy (n=41,986)**	**Brachytherapy (n=10,259)**	**Surgery (n=84,031)**	**No definitive therapy (n=32,336)**
Baseline				
Age; mean (SD)	70.6 (7.0)	66.7 (7.8)	65.7 (9.1)	73.4 (9.0)
Race; *n* (%)				
White	33,089 (80.5)	8,960 (87.3)	72,629 (86.4)	26,289 (81.3)
Black	5,060 (12.1)	888 (8.7)	8,043 (9.6)	3,992 (12.3)
Other	3,117 (7.4)	411 (4.0)	3,359 (4.0)	2,055 (6.4)
Grade; *n* (%)				
Well differentiated	4,296 (10.2)	659 (6.4)	12,733 (15.2)	3,922 (12.1)
Moderately differentiated	28,689 (68.3)	8,871 (86.5)	55,899 (66.5)	20,829 (64.4)
Poorly differentiated	8,858 (21.1)	721 (7.0)	15,098 (18.0)	7,464 (23.1)
Undifferentiated, anaplastic	143 (0.3)	8 (0.1)	301 (0.4)	121 (0.4)
Comorbidity; *n* (%)	1,248 (3.0)	87 (0.8)	0 (0.0)	647 (2.0)
Follow-up				
Acute myeloid leukemia (AML); *n* (%)	72 (0.2)	5 (0.1)	82 (0.1)	25 (0.1)
Total person-years contributed to cohort	258,717	44,126	596,642	165,335
AML incidence density; cases/person-years	28/100,000	11/100,000	14/100,000	15/100,000
Duration of follow-up (years); median (IQR)	5.6 (3.2, 8.7)	3.8 (2.4, 5.7)	6.6 (3.6, 10.2)	4.4 (2.6, 7.1)
Lost to follow-up; *n* (%)	367 (0.9)	101 (1.0)	852 (1.0)	539 (1.7)
Deceased during follow-up; *n* (%)	10,922 (26.0)	600 (5.8)	18,102 (21.5)	10,855 (33.6)

Table 3. Relative risk of developing acute myeloid leukemia among patients with localized or locally advanced prostate adenocarcinoma in the United States.

Treatment	Unadjusted Relative Risk (95% Confidence Interval)	Adjusted Relative Risk* (95% Confidence Interval)
External beam radiation therapy	1.74 (1.10, 2.74)	2.05 (1.29, 3.26)
Brachytherapy	0.80 (0.31, 2.10)	1.22 (0.46, 3.22)
Surgery	0.82 (0.52, 1.29)	1.24 (0.77, 1.98)
No definitive therapy	Reference	Reference

*Adjusted for age at diagnosis, ethnicity, grade, and comorbidity.

Table 4. Number of patients with localized prostate adenocarcinoma needed to treat with external beam radiation therapy or brachytherapy for one case of acute myeloid leukemia to develop during 5-year intervals of follow-up.

	Number needed to treat (harm)		
	5-year	**10-year**	**15-year**
External beam radiation therapy	1505	527	333
Brachytherapy	3433	1198	†

†Insufficient data to estimate number needed to treat (harm).

CHAPTER 4

MYELOMA

Introduction

Myeloma is the second most common hematologic malignancy in the United States.[16] This plasma cell malignancy is characterized by extensive genetic and chromosomal abnormalities.[16] Myeloma is difficult to treat and confers a poor prognosis; the median survival is 3 – 7 years depending on therapeutic course.[16] Ionizing radiation, such as that used in radiation therapy, may have a role in myelomagenesis through radiation-induced genomic and chromosomal instability.[75,76] Radiation therapy (as external beam radiation therapy [EBRT] or brachytherapy) is one of the main therapeutic options for localized or locally advanced prostate cancer.[3,53] Prostate irradiation may result in unintentional radiation exposure to the pelvis, which contains a high concentration of active bone marrow in adults,[20] an exposure that may be relevant to myeloma incidence and a potential threat to prostate cancer patients treated with radiation therapy. Therefore, we investigated the effect of radiation therapy (EBRT alone or brachytherapy alone) on myeloma incidence in a population-based cohort of 168,612 patients with localized or locally advanced prostate adenocarcinoma.

Methods

Study population

The data used for this analysis have been previously described[77]. Briefly, we used data from 9 Surveillance, Epidemiology, and End Results (SEER) registries[38] to identify eligible patients. Men with newly diagnosed localized or locally advanced prostate adenocarcinoma between January 1988 and December 2003, with extended follow-up through December 2004, who were treated with EBRT, brachytherapy, surgery, or no definitive therapy and survived >1 year after prostate cancer diagnosis were eligible for our analyses. Patients with localized or locally advanced prostate adenocarcinoma were identified according to the International Classification of Diseases for Oncology 3rd Edition (ICD-O-3) histology code for adenocarcinoma (8140)[40] and the SEER historic stage designation of 'local/regional', which allows consistent definitions of stage over time[39].

Variables

We used the ICD-O-3 definition of myeloma for our outcome, which includes solitary plasmacytomas and multiple myeloma.[40] The SEER database contained information regarding initial therapy for each patient. These data were used to create a categorical variable for initial therapy that consisted of mutually exclusive categories for EBRT alone, brachytherapy alone, surgery alone, and no definitive therapy (i.e. no radiation therapy or surgery [reference category]).

A minimal sufficient set of covariates for which to adjust in the analyses were identified *a priori* using the back-door criterion in a directed acyclic graph (DAG)[46-48] which encoded risk factors for myeloma incidence and clinical characteristics that guide treatment decisions for localized or locally advanced prostate adenocarcinoma[3,53,78-85]. Our DAG (*Figure 2*) indicated that adjustment for age at prostate cancer diagnosis, race, prostate cancer grade, and comorbidity could reduce confounding bias when estimating the effect of radiation therapy on myeloma incidence. Consequently, age at diagnosis was included as a continuous variable in our analyses. The patient's race was categorized as White (reference category), Black, or Other. Prostate cancer grade was categorized according to the American Joint Classification on Cancer guidelines for grading tumors (Grade I: Well-differentiated [reference category]; Grade II: Moderately differentiated, Grade III: Poorly differentiated; Grade IV: Undifferentiated).[59] Comorbidity was defined as physician-determined presence of comorbidity at the time of diagnosis that precluded surgery as a therapeutic option.

Data analysis

Cox proportional hazards regression with censored observations was used to estimate the hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) of myeloma incidence following EBRT alone, brachytherapy alone, and surgery alone compared to no definitive therapy after adjusting for age at

diagnosis, race, grade, and comorbidity. Furthermore, we estimated the effect of EBRT on myeloma incidence by duration of follow-up (≤10 years/>10 years) based on evidence of increased radiation-induced myelomagenesis after 10 years[76]. Insufficient data were available to estimate the long-term (>10 years) effect of brachytherapy on myeloma incidence. Person-time was measured in years from the date of prostate cancer diagnosis. Patients who did not develop myeloma were censored at the time of last follow-up, incident malignancy other than myeloma, or death. The proportionality assumption was evaluated by graphing and examining interaction terms in the model; no violations were detected.

Results

Our study population consisted of 168,612 men with localized or locally advanced prostate adenocarcinoma. Patients who were not treated with definitive therapy were older (mean age=73.4, standard deviation [SD]=9.0) than patients treated with EBRT (mean age=70.6, SD=7.0), brachytherapy (mean age=66.7, SD=7.8), or surgery (mean age=65.7, SD=9.1). The brachytherapy group had the lowest proportion of Blacks (brachytherapy=8.7%, surgery=9.6%, EBRT=12.1%, no definitive therapy=12.3%) and the lowest proportion of high grade tumors (poorly differentiated or undifferentiated) at diagnosis compared to the other treatment groups (brachytherapy=7.1%, surgery=18.4%, EBRT=21.4%, no definitive therapy=23.5%).

This cohort yielded 344 incident myeloma cases during 1,064,820 person-years of follow-up after prostate adenocarcinoma diagnosis. The brachytherapy group accrued the shortest duration of follow-up (median=3.8 years, inter-quartile range [IQR]=2.4, 5.7) compared to other treatment groups, whereas the surgery group accrued the longest duration of follow-up (median=6.6 years, IQR=3.6, 10.2). The highest proportionate mortality during follow-up was observed in the no definitive therapy group compared to the other treatment groups (no definitive therapy=33.6%, EBRT=26.0%, surgery=21.5%, brachytherapy=5.8%). *Table 5* provides detailed baseline and follow-up characteristics for this cohort by treatment group.

The adjusted relative hazards of myeloma incidence following EBRT and surgery were similar to the no definitive therapy group (EBRT: HR=0.97, 95% CI 0.70, 1.35; surgery: HR=1.02, 95% CI: 0.75, 1.39), whereas the relative hazard of myeloma incidence following brachytherapy was lower than the no definitive therapy group (brachytherapy: HR=0.60, 95% CI: 0.28, 1.33). Furthermore, the effect of EBRT on myeloma incidence appeared to decrease with prolonged follow-up (≤10 years: HR=1.15, 95% CI: 0.83, 1.61; >10 years: HR=0.52, 95% CI: 0.13, 2.19). *Table 6* details the relative hazards and corresponding 95% confidence intervals by treatment type.

Discussion

This report extends our efforts to evaluate biologically plausible hematologic consequences of radiation therapy among prostate cancer patients while considering the potential for differential radiosensitivity of cells derived from hematopoietic progenitors[8] and expands on our previous findings[77] of increased relative and absolute risks of acute myeloid leukemia following EBRT among patients with localized or locally advanced prostate adenocarcinoma. Our results indicate that neither EBRT alone nor brachytherapy alone increases the relative hazard of myeloma incidence among patients with localized or locally advanced prostate adenocarcinoma. The point estimate for brachytherapy actually suggests an inverse relation to myeloma incidence. However, this point estimate may be misleading because of sparse-data bias (known to induce a bias away from the null[27$^{p.263}$]) attributable to few incident myeloma cases in this group. Our results also indicate that the effect of EBRT on myeloma incidence is not increased among patients followed >10 years after prostate cancer diagnosis.

Our overall results are consistent with the few previous analyses[22,23,61] that evaluated myeloma incidence following radiation therapy among prostate cancer patients. However, the distinction between comparison groups in previous analyses and our analysis should be emphasized within the context of the ultimate question being posed by this investigation: Would patients with localized or locally advanced prostate adenocarcinoma who were treated with radiation therapy have assumed the risk (of myeloma incidence) of patients with localized

or locally advanced prostate adenocarcinoma who were untreated if the former group had not been treated with radiation therapy? This question represents a counterfactual contrast, which provides a framework for drawing meaningful inferences from data[27[p.54-55],28[p.137-138]-30]. Clearly, this ideal comparison is unachievable because the same person cannot be simultaneously exposed and unexposed to radiation therapy, which is why comparison groups are substituted to represent this ideal as closely as possible. Previous analyses[22,23,61] estimated standardized incidence ratios (SIRs) by comparing myeloma incidence between prostate cancer patients treated with radiation therapy to the general population, whereas our analysis estimated hazard ratios of myeloma incidence by comparing patients treated with radiation therapy to patients who were not treated with definitive therapy. Comparisons to the general population are poor representations of the counterfactual contrast in this scenario; a lack of exposure to radiation therapy does not necessarily qualify the general population as a valid comparison group when estimating treatment effects. Individuals in the general population do not have a primary diagnosis of localized or locally advanced prostate adenocarcinoma and are subsequently ineligible for prostate irradiation. Therefore, the general population is a non-comparable entity and estimates derived from comparisons to the general population offer limited insight regarding the effect of radiation therapy on myeloma incidence among prostate cancer patients. Furthermore, factors other than those used to standardize the comparison groups contribute to disparate baseline risk of myeloma between

patients with prostate cancer and the general population. Consequently, residual confounding would threaten the validity of previous estimates even if the general population were an appropriate comparison group.[27[p.69]]

Cuzick et al.[76] suggested that an increased relative risk of myeloma following radiation therapy for solid tumors may not be evident until 10 – 30 years after radiation, but this long empirical induction period poses a challenge when evaluating prostate cancer patients because of older age at diagnosis and thus reduced sample sizes with prolonged duration of follow-up. For example, the results by McMaster et al.[61] indicated a marked increase in the relative risk of myeloma following EBRT for patients who survived ≥20 years (SIR=4.11). However, this SIR estimate was based on 4 myeloma cases and likely unstable because of sparse data. Our stratified analysis indicated a decreased relative hazard of myeloma incidence following EBRT for patients with localized or locally advanced prostate adenocarcinoma followed more than 10 years, but this estimate also lacks durability, evident by the large confidence limit ratio[86]. Ultimately, the combination of a long empirical induction period and older age at diagnosis may further diminish the concern regarding myeloma incidence following radiation therapy for most patients with localized or locally advanced prostate adenocarcinoma, but additional data are needed for patients with long life expectancy after prostate adenocarcinoma diagnosis.

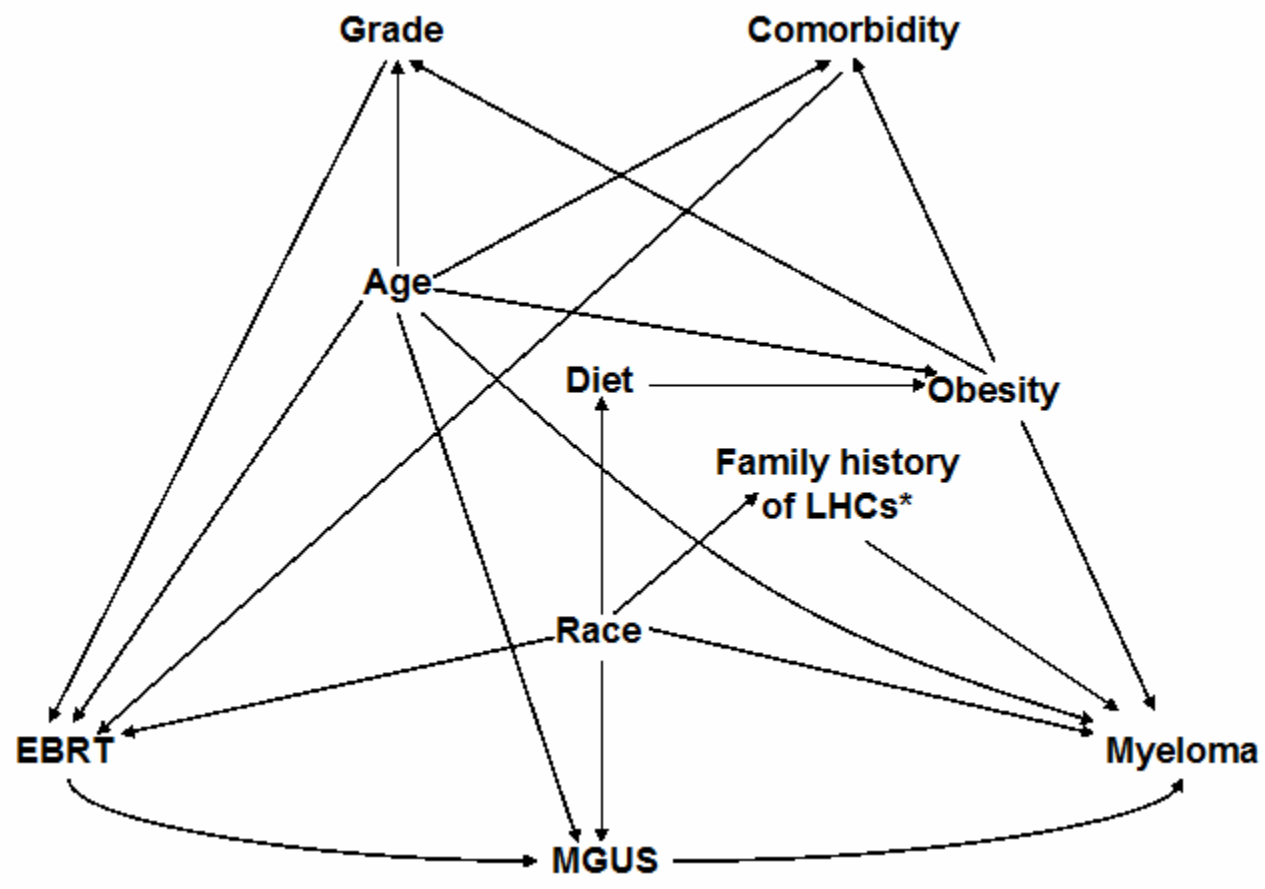
Although our results did not indicate an increased relative hazard of myeloma incidence following radiation therapy among patients with localized or

locally advanced prostate adenocarcinoma, recent evidence may provide insight regarding our findings. Iwanaga et al.[87] reported a positive association between ionizing radiation and monoclonal gammopathy of undetermined significance (MGUS), a pre-malignant plasma cell disorder, and a longitudinal study by Landgren et al.[88] indicated that MGUS consistently precedes myeloma incidence. These combined findings suggest that a positive relation between EBRT and myeloma incidence is plausible. However, MGUS is related to several malignant and non-malignant causes of death other than myeloma.[89] Consequently, our estimates for the effect of radiation therapy on myeloma incidence could have incurred a bias toward the null (i.e. no apparent effect of radiation therapy) if myeloma incidence were associated with loss to follow-up from MGUS-related competing risks and this loss occurred more frequently among patients treated with radiation therapy than patients who were not treated with definitive therapy (i.e. selective loss to follow-up). Unfortunately, we were unable to quantitatively evaluate the potential impact of MGUS-related competing risks because data regarding MGUS are unavailable in the SEER database. Adequately powered longitudinal studies which determine MGUS and myeloma status may be able to provide further insight regarding this phenomenon.

In summary, our results indicate that neither EBRT nor brachytherapy increases the relative hazard of myeloma incidence among patients with localized or locally advanced prostate adenocarcinoma. Despite a previous suggestion that myeloma incidence may be a concern >10 years after radiation

therapy,[76] our results indicate that the effect of EBRT on myeloma incidence is not increased among patients followed >10 years after prostate cancer diagnosis. These results are particularly important for raising awareness that our previous findings[77] regarding increased relative and absolute risks of acute myeloid leukemia following EBRT among patients with localized or locally advanced prostate adenocarcinoma should not be generalized to other hematologic outcomes. Independent evaluations of potential hematologic outcomes which consider the underlying etiologic pathways and this unique population at risk may reveal considerable variation in relative risks and clinical relevance.

Figure 2. Proposed influence structure for the relation between external beam radiation therapy (EBRT) and myeloma incidence among patients with localized or locally advanced prostate adenocarcinoma.



Note: MUGS: Monoclonal gammopathy of undetermined significance; LHCs: lymphohematopoietic cancers

Table 5. Characteristics of patients diagnosed with localized or locally advanced prostate adenocarcinoma in the Surveillance, Epidemiology, and End Results database; 1988-2003.

Variable	**External beam radiation therapy (n=41,986)**	**Brachytherapy (n=10,259)**	**Surgery (n=84,031)**	**No definitive therapy (n=32,336)**
Baseline				
Age; mean (SD)	70.6 (7.0)	66.7 (7.8)	65.7 (9.1)	73.4 (9.0)
Race; *n* (%)				
White	33,089 (80.5)	8,960 (87.3)	72,629 (86.4)	26,289 (81.3)
Black	5,060 (12.1)	888 (8.7)	8,043 (9.6)	3,992 (12.3)
Other	3,117 (7.4)	411 (4.0)	3,359 (4.0)	2,055 (6.4)
Grade; *n* (%)				
Well differentiated	4,296 (10.2)	659 (6.4)	12,733 (15.2)	3,922 (12.1)
Moderately differentiated	28,689 (68.3)	8,871 (86.5)	55,899 (66.5)	20,829 (64.4)
Poorly differentiated	8,858 (21.1)	721 (7.0)	15,098 (18.0)	7,464 (23.1)
Undifferentiated, anaplastic	143 (0.3)	8 (0.1)	301 (0.4)	121 (0.4)
Comorbidity; *n* (%)	1,248 (3.0)	87 (0.8)	0 (0.0)	647 (2.0)
Myeloma cases; *n* (%)	90 (0.2)	7 (0.1)	184 (0.2)	63 (0.2)
Total person-years contributed to cohort	258,717	44,126	596,642	165,335
Myeloma incidence density; cases/person-years	35/100,000	16/100,000	31/100,000	38/100,000
Duration of follow-up (years); median (IQR)	5.6 (3.2, 8.7)	3.8 (2.4, 5.7)	6.6 (3.6, 10.2)	4.4 (2.6, 7.1)
Lost to follow-up; *n* (%)	367 (0.9)	101 (1.0)	852 (1.0)	539 (1.7)
Deceased during follow-up; *n* (%)	10,922 (26.0)	600 (5.8)	18,102 (21.5)	10,855 (33.6)

Table 6. Relative hazards of myeloma incidence by therapeutic approach among patients with localized or locally advanced prostate adenocarcinoma.

Treatment	Unadjusted Hazard Ratio (95% Confidence Interval)	Adjusted Hazard Ratio* (95% Confidence Interval)
External beam radiation therapy	0.86 (0.62, 1.19)	0.97 (0.70, 1.35)
≤10 years follow-up	1.01 (0.73, 1.41)	1.15 (0.83, 1.61)
>10 years follow-up	0.52 (0.13, 2.19)	0.52 (0.13, 2.19)
Brachytherapy	0.45 (0.20, 0.98)	0.60 (0.28, 1.33)
Surgery	0.73 (0.54, 0.97)	1.02 (0.75, 1.39)
No definitive therapy	1.00 (Reference)	1.00 (Reference)

*Adjusted for age at diagnosis, race, grade, and comorbidity.

CHAPTER 5

SUMMARY

Our analysis of a population-based cohort of 168,612 men with localized or locally advanced prostate adenocarcinoma indicates that the relative risk of developing acute myeloid leukemia following definitive therapy with EBRT is 105% greater than no definitive therapy, but the relative risk of acute myeloid leukemia following brachytherapy is 83% lower than EBRT. Furthermore, the absolute effect of EBRT on acute myeloid leukemia incidence is more than 2-fold greater than brachytherapy. Our findings are useful for promoting recognition that acute myeloid leukemia may be an adverse consequence that is relevant to patients treated with EBRT for localized or locally advanced prostate adenocarcinoma.

Furthermore, our results indicate that neither EBRT nor brachytherapy increases the relative hazard of myeloma incidence among patients with localized or locally advanced prostate adenocarcinoma. Despite a previous suggestion that myeloma incidence may be a concern >10 years after radiation therapy,[76] our results indicate that the effect of EBRT on myeloma incidence is not increased among patients followed >10 years after prostate cancer diagnosis. These results are particularly important for raising awareness that our findings[77] regarding increased relative and absolute risks of acute myeloid leukemia following EBRT among patients with localized or locally advanced

prostate adenocarcinoma should not be generalized to other hematologic outcomes. Independent evaluations of potential hematologic outcomes which consider the underlying etiologic pathways and this unique population at risk may reveal considerable variation in relative risks and clinical relevance.

Our investigation addresses several limitations of previous studies regarding acute myeloid leukemia and myeloma incidence following EBRT among prostate cancer patients. Our use of 16 years of SEER data allowed us to have a large sample size (*n*=168,612) representative of prostate cancer cases in the United States with sufficient power to detect the effects of EBRT on rare outcomes (90% power to detect a hazard ratio of 1.03 for acute myeloid leukemia or myeloma following EBRT). The SEER database is renowned for its high case ascertainment rates (>97%) and vigilant monitoring of data quality to obtain and maintain accurate information.[90] High case ascertainment rates reduce the probability of incurring front-end selection bias in our investigation and uniform follow-up procedures by the SEER registries decreases the probability of incurring selective loss to follow-up, evident by the empirically low rates of loss to follow-up in our analyses (<2.0%). The SEER program's thorough attention to obtaining and maintaining high quality data may also be helpful for reducing potential misclassification of exposures, outcomes, and potential confounders. Furthermore, our choice to restrict the study period to 1988-2003 contrasts previous studies that utilized all years in the SEER database (since 1973), but may be beneficial because prostate cancer coding schemes were uniform in the

database throughout this period,[39] which may further support consistent classification of relevant variables. The selected period also represents contemporary prostate cancer detection and management paradigms and would thus yield information with current relevance.[91]

The designation of an appropriate reference group is critical for evaluating causal effects.[27[p.54-55],28[p.137-138]-30] Our investigation has the distinct advantage of designating comparison groups that may facilitate causal inferences regarding the effects of EBRT on acute myeloid leukemia and myeloma incidence among patients with localized or locally advanced prostate adenocarcinoma, whereas previous studies designated comparison groups that were inadequate representations of the counterfactual and thus offer limited evidence regarding causality. Nearly all of the previous studies[22,23,25,61] compared acute myeloid leukemia and myeloma incidence following EBRT among prostate cancer patients to the general population. However, the general population does not represent an appropriate counterfactual contrast because it does not consist of patients with prostate cancer for whom EBRT could be administered. In contrast, we designated patients who were not treated with EBRT or surgery as the reference group to facilitate causal inferences because these patients most closely represent the natural course of localized or locally advanced prostate adenocarcinoma, which allows meaningful estimates of relative risk.

The restriction of our study population to patients with localized prostate cancer at baseline may also improve interpretation regarding the effect of

prostate-directed EBRT on acute myeloid leukemia and myeloma incidence. Previous studies[22-25,61] have included patients with all stages of prostate cancer in the analyses. A combined study population that includes localized and metastatic cases may obscure interpretations regarding the effect of prostate-directed EBRT on these malignancies. EBRT for localized prostate cancer is administered to the prostate with potential unintended radiation exposure to the pelvic region surrounding the prostate,[20] whereas EBRT for metastatic prostate cancer is administered for site-specific palliation[32] with potential unintended radiation exposure to various anatomic locations (bone or soft tissue), which exposes lower concentrations of hematopoietic stem cells to the mutagenic effects of radiation. A study population restricted to patients with localized or locally advanced prostate cancer, as in our analyses, increases the likelihood that EBRT targeted the prostate, which subsequently improves interpretation regarding the effect of EBRT on acute myeloid leukemia and myeloma incidence because all patients received radiation to the same anatomic location.

An additional consideration regarding our findings is that the SEER database lacks information regarding radiation dose and thus dose-response estimation was beyond the scope of our proposed investigation. Information regarding radiation dose could have been useful for identifying threshold effects. However, evidence indicates that patients in our cohort who were treated with EBRT would have uniformly reached a minimum threshold for radiation-induced DNA damage. Conventional EBRT for localized prostate cancer delivers a

cumulative dose of 64-70 Grays (Gy) to the prostate and this range has been used since the mid-1980's,[92[p.343]] which includes our study period. Recent reports indicate that higher doses (70-81 Gy) may be used to improve biochemical control, but these doses have not been widely incorporated into clinical practice.[93-95] A dose of 64 Gy, the minimum anticipated for patients in our cohort, results in ~4.0 Gy of radiation exposure to the bone marrow, which is sufficient to induce DNA damage.[20] These data only account for the direct effects of radiation. The indirect effects of radiation (i.e. radiation-induced genomic instability and radiation-induced bystander effects) occur at even lower doses.[96] Furthermore, a linear no-threshold perspective of radiation carcinogenesis[72] would imply that any dose is capable of inducing mutations relevant to acute myeloid leukemia or myeloma. Although these data indicate that threshold effects may not be an issue in our investigation, higher doses may increase the rate of malignant transformation[20] and this potential effect modification cannot be addressed without information regarding radiation dose. Therefore, our relative risk estimates may represent an average effect of EBRT on acute myeloid leukemia and myeloma incidence.

Ultimately, a comprehensive documentation of all malignant outcomes (hematologic or solid tumor) potentially related to radiation therapy may facilitate risk/benefit profiling for patients with localized or locally advanced prostate adenocarcinoma and thus lead to informed decisions regarding therapeutic approach. Analysts should thoroughly consider the comparison groups being

used and the exposure-outcome structure when performing future studies of second malignancies following EBRT. In addition to comprehensively documenting all relevant second malignancies, future research on this topic should focus on evaluating potential effect modifiers. For example, the effect of EBRT on acute myeloid leukemia or myeloma could be modified by pre-existing genetic abnormalities. Consequently, predisposing factors could warrant alternate therapeutic approaches as a high-risk prevention strategy. The demands on sample size and resources required for data collection for an analysis of effect modification effectively precludes traditional cohort or case-control designs. However, case-only analyses offer an alternate study design by which to examine effect modification in this scenario, particularly related to genetic modifiers. The efficient design of case-only analyses results in fewer demands on sample size and resources for data collection. Analysts should consider implementing this feasible design to generate potentially valuable evidence that could be useful for guiding treatment decisions of patients with localized or locally advanced prostate adenocarcinoma.

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APPENDICES

APPENDIX A

Human Subject Research Training and Health Information Portability and Accountability Act Certification

CITI Collaborative Institutional Training Initiative

Human Research Curriculum Completion Report
Printed on Tuesday, May 6, 2008

Learner: Rohit Ojha (username: rojha)
Institution: University of North Texas Health Science Center
Contact Information Phone: 817-735-5029
Email: rojha@hsc.unt.edu
Social-Behavioral: These modules concentrate on social and behavioral studies that do not involve biomedical interventions. Faculty and students conducting research within the School of Public Health (SPH) and School of Health Professions (SPH) are likely participants in this Learner Group.

Stage 1. Basic Course Passed on 05/06/08 (Ref # 1784446)

Required Modules	Date Completed
Belmont Report and CITI Course Introduction	05/06/08
History and Ethical Principles - SBR	05/06/08
Defining Research with Human Subjects - SBR	05/06/08
The Regulations and The Social and Behavioral Sciences - SBR	05/06/08
Assessing Risk in Social and Behavioral Sciences - SBR	05/06/08
Informed Consent - SBR	05/06/08
Privacy and Confidentiality - SBR	05/06/08
Research with Prisoners - SBR	05/06/08
Research with Children - SBR	05/06/08

Certificate of Completion

This certifies that

Rohit Ojha

has successfully completed

HIPAA Training

on

Friday, October 31, 2008 12:38 PM

UNIVERSITY of NORTH TEXAS
HEALTH SCIENCE CENTER at Fort Worth
★
Education, Research, Patient Care and Service

APPENDIX B

Institutional Review Board Approvals

UNIVERSITY of NORTH TEXAS
HEALTH SCIENCE CENTER at Fort Worth
★
Education, Research,
Patient Care and Service

DATE: 28 February 2008

Office for the Protection of Human Subjects
3500 Camp Bowie Boulevard
Fort Worth, Texas 76107-2699

TO: Lori Fischbach, PhD, MPH
with Rohit P. Ojha, MPH
Department of Epidemiology
School of Public Health

PROTOCOL: #2008-16

"Prostate Cancer Treatment and Risk of Acute Myeloid Leukemia in a Population-Based Prospective Cohort"

IRB BOARD ACTION AND NOTICE OF APPROVAL

The Institutional Review Board (IRB) of the University of North Texas Health Science Center (UNTHSC) has reviewed your protocol and has granted approval for **EXEMPT** status (as specified in Federal Regulations 45 CFR 46.101(b), category (4).

Note that you are responsible for complying with all UNTHSC IRB and OPHS policies, decisions, conditions and requirements regarding projects involving human subjects. You are responsible for insuring that the research is implemented as specified in the approved protocol. Unless otherwise authorized by the UNTHSC-IRB, you are responsible for notifying subjects that their participation and information will be used for research purposes. In addition, you are required to use ONLY the IRB approved documents, materials and/or process designated for this protocol.

You must report to the Chair of the IRB any changes affecting the protocol upon which this certification is based. **No changes may be made without prior approval by the IRB** except those necessary to eliminate immediate hazards.

If you have any questions, please contact Ms. Sharon Wolff, IRB Compliance Coordinator, at phone (817) 735-5457 in the Office for the Protection of Human Subjects, or send email to her at stobola@hsc.unt.edu

Sincerely,

Brian Gladue, PhD
Chair, UNTHSC Institutional Review Board

cc: S. Wolff, OPHS

UNIVERSITY *of* NORTH TEXAS HEALTH SCIENCE CENTER *at Fort Worth*
TEXAS COLLEGE OF OSTEOPATHIC MEDICINE
INSTITUTIONAL REVIEW BOARD FOR THE PROTECTION OF HUMAN SUBJECTS

BOARD ACTION

IRB PROJECT #: 2008-16 DATE SUBMITTED: February 2008

PRINCIPAL INVESTIGATOR: Lori Fischbach, PhD, MPH (with doctoral student Rohit P. Ojha, MPH)

PROJECT TITLE: Prostate Cancer Treatment and Risk of Acute Myeloid Leukemia in a Population-Based Prospective Cohort

PROTOCOL #: _____

DEPARTMENT: Epidemiology / SPH TELEPHONE EXTENSION: _____

In accordance with UNT Health Science Center policy on the protection of human subjects, the following action has been taken on the above referenced project:

Approval, when given, is **only** for the project as submitted. **No changes** may be implemented without first receiving IRB review and approval.

_____ Project has received approval through _____.

_____ Informed Consent approved as submitted on _____. You **MUST** use this version (attached) rather than previously approved versions. In addition, only consent documents which bear the official UNTHSC IRB approval stamp can be used with subjects.

_____ Study Protocol dated _____ approved as submitted.

_____ Protocol Synopsis approved as submitted on _____.

_____ Amendment _____ to the protocol approved as submitted.

_____ Based upon the recently completed Continuing Review (IRB Form 4), project has received continued approval through _____.

_____ Project has been reviewed. In order to receive approval, you must incorporate the attached modifications. You must submit one "highlighted" copy and one "clean" copy of the revised protocol synopsis, informed consent and advertisements to the IRB for review. YOU MAY NOT BEGIN YOUR PROJECT UNTIL NOTIFIED BY THE IRB.

_____ Consideration of the project has been tabled pending resolution of the issue(s) outlined below.

_____ Project is disapproved for the reason(s) outlined below.

_____ Completion of project is acknowledged and all required paperwork has been received.

___✓___ Special Findings:

Project qualifies for Exempt status under the provisions of 45 CFR 46.101 (b) category (4) research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if the sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

Chairman, Institutional Review Board

February 28, 2008
Date

IRB Form 2 revised 12-03 MA 04-1487

UNIVERSITY of NORTH TEXAS
HEALTH SCIENCE CENTER at Fort Worth
★
Education, Research,
Patient Care and Service

DATE: 20 April 2010

Office for the Protection of Human Subjects
3500 Camp Bowie Boulevard
Fort Worth, Texas 76107-2699

TO: Karan Singh, PhD
with Rohit Ojha, DrPH (ABD), MPH
Department of Biostatistics
School of Public Health

PROTOCOL: #2010-061

"External Beam Radiation Therapy for Localized or Locally Advanced Prostrate Adenocarcinoma and Myeloma Incidence in a Population-Based Cohort"

IRB BOARD ACTION AND NOTICE OF APPROVAL

The Institutional Review Board (IRB) of the University of North Texas Health Science Center (UNTHSC) has reviewed your protocol and has granted approval for **EXEMPT** status as specified in Federal Regulations 45 CFR 46.101(b), category (4).

Note that you are responsible for complying with all UNTHSC IRB and OPHS policies, decisions, conditions and requirements regarding projects involving human subjects. You are responsible for insuring that the research is implemented as specified in the approved protocol. Unless otherwise authorized by the UNTHSC-IRB, you are responsible for notifying subjects that their participation and information will be used for research purposes. In addition, you are required to use ONLY the IRB approved documents, materials and/or process designated for this protocol.

You must report to the Chair of the IRB any changes affecting the protocol upon which this certification is based. **No changes may be made without prior approval by the IRB** except those necessary to eliminate immediate hazards.

If you have any questions, please contact Ms. Itzel Peña, Human Subject Protection Coordinator, at phone (817) 735-0673 in the Office for the Protection of Human Subjects, or send email to her at Itzel.Pena@unthsc.edu

Sincerely,

Brian Gladue, PhD
Chair, UNTHSC Institutional Review Board

cc: I. Peña, OPHS

UNIVERSITY of NORTH TEXAS HEALTH SCIENCE CENTER at Fort Worth
TEXAS COLLEGE OF OSTEOPATHIC MEDICINE
INSTITUTIONAL REVIEW BOARD FOR THE PROTECTION OF HUMAN SUBJECTS

BOARD ACTION

IRB PROJECT #: 2010-061 DATE SUBMITTED: April 19, 2010

PRINCIPAL INVESTIGATOR: Karan Singh, Ph.D. with Rohit Ojha DrPH (ABD), MPH

PROJECT TITLE: External Beam Radiation Therapy for Localized Advanced Prostrate Adenocarcinoma and Myeloma Incidence in a Population-Based Cohort

PROTOCOL #: _____

DEPARTMENT: Biostatistics/ SPH TELEPHONE EXTENSION: _____

In accordance with UNT Health Science Center policy on the protection of human subjects, the following action has been taken on the above referenced project:

Approval, when given, is **only** for the project as submitted. **No changes** may be implemented without first receiving IRB review and approval.

_____ Project has received approval through _____.

_____ Informed Consent approved as submitted on _____. You **MUST** use this version (attached) rather than previously approved versions. In addition, only consent documents which bear the official UNTHSC IRB approval stamp can be used with subjects.

_____ Study Protocol dated _____ approved as submitted.

_____ Protocol Synopsis approved as submitted on _____.

_____ Amendment _____ to the protocol approved as submitted.

_____ Based upon the recently completed Continuing Review (IRB Form 4), project has received continued approval through _____.

_____ Project has been reviewed. In order to receive approval, you must incorporate the attached modifications. You must submit one "highlighted" copy and one "clean" copy of the revised protocol synopsis, informed consent and advertisements to the IRB for review. YOU MAY NOT BEGIN YOUR PROJECT UNTIL NOTIFIED BY THE IRB.

_____ Consideration of the project has been tabled pending resolution of the issue(s) outlined below.

_____ Project is disapproved for the reason(s) outlined below.

_____ Completion of project is acknowledged and all required paperwork has been received.

___✓___ Special Findings:

This project has been approved as Exempt Category Research under the provisions of 45 CFR 46. 101 (b) Category (4) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

_____ April 20, 2010

Chairman, Institutional Review Board Date

IRB Form 2 revised 12-03 MA 04-1487

APPENDIX C

Reference Style Approval

UNIVERSITY of NORTH TEXAS
HEALTH SCIENCE CENTER at Fort Worth

Education, Research,
Patient Care and Service

October 25, 2010

University of North Texas Health Science Center
School of Public Health
Department of Epidemiology
3500 Camp Bowie Blvd.
Fort Worth, TX 76107

RE: Permission to modify reference style for dissertation

The formatting guidelines for the University of North Texas Health Science Center, School of Public Health currently suggest using the 5th edition of the Publication Manual of the American Psychological Association (APA style guide) for referencing. However, other formats may be used if the content is to be submitted for publication. Rohit P. Ojha has requested permission to utilize the American Medical Association (AMA) style because the content from his dissertation has already been published or is currently in press in journals formatted according to the AMA guidelines. We hereby grant Rohit permission to utilize AMA reference style for his dissertation to maintain consistency with his publications and avoid potential copyright violations.

Chair, Department of Epidemiology

Major Professor

Texas College of Osteopathic Medicine • Graduate School of Biomedical Sciences • School of Public Health • School of Health Professions
Institutes for Discovery • University of North Texas Physicians Group
3500 Camp Bowie Boulevard, Fort Worth, Texas 76107-2699 • 817-735-2000