Radiotherapy and Oncology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Pattern of solid and hematopoietic second malignancy after local therapy for prostate cancer

Chenyang Wang *, Christopher R. King, Mitchell Kamrava, Keisuke S. Iwamoto, Allen M. Chen, Daniel Low, Patrick A. Kupelian, Michael L. Steinberg

Department of Radiation Oncology, University of California, Los Angeles, Los Angeles, CA, United States

ARTICLE INFO

Article history:
Received 30 October 2016
Received in revised form 9 January 2017
Accepted 9 January 2017
Available online xxxx

Keywords:
Prostate cancer
Second malignancy
External beam radiotherapy
Brachytherapy

ABSTRACT

Background and purpose: Second malignancies (SM) after external beam radiotherapy (EBRT) or brachytherapy (BT) for prostate cancer (PCa) are rare but serious sequelae.
Materials and methods: The Surveillance, Epidemiology, and End Results (SEER) database was used to identify men diagnosed with cT1-2N0M0 PCa between 1999 and 2005, who underwent EBRT, BT or radical prostatectomy (RP). Patients with time interval to second malignancy or follow-up shorter than five and two years were excluded for solid and hematopoietic SM analyses respectively. Risks for solid and hematopoietic SM were evaluated via the multivariate Fine and Gray proportional hazards model.
Results: EBRT and BT resulted in similar increases in solid and hematopoietic SM compared to RP. In subgroup analysis stratified by treatment modality, only the EBRT cohort demonstrated significantly decreased solid and hematopoietic SM in years 2002–2005 compared to years 1999–2001, with adjusted-hazard ratios of 0.752 ($p = 0.001$) and 0.815 ($p = 0.018$) respectively.
Conclusions: EBRT and BT resulted in statistically equivalent increase in both solid and hematopoietic SM compared to RP. EBRT in more recent years resulted in significantly decreased solid and hematopoietic SM, coinciding with increased utilization of IMRT.
 Radiotherapy and Oncology xxx (2017) xxx–xxx

The fact that prostate cancer (PCa) patients who underwent radiotherapy (RT) have increased second malignancy (SM) risk has been established by multiple studies [1–8], with carcinomas of the bladder, rectum, lung and sarcoma being the most common SM [3]. External beam radiotherapy (EBRT) for PCa has seen significant technological advances over the past decade, with intensity-modulated radiotherapy (IMRT) gradually replacing 3D conformal radiotherapy (3D-CRT) [9]. IMRT allows for dose-escalation to the target while reducing dose to adjacent organs such as the bladder and rectum [9,10], and recent prospective study demonstrated improved biochemical control [11] while a retrospective study demonstrated improved overall survival associated with radiation dose-escalation [12]. Meanwhile, IMRT also potentially results in higher total integral and peripheral dose due to multiple entry angles, longer beam-on times, more internal and multi-leaf collimator scatter, linear accelerator head leakage and neutron contamination [13,14]. As a result, a larger volume of normal tissue receives low-dose radiation, which has been theorized to increase SM risk in tissue encompassed within the dose–volume histogram (DVH) [13,15]. However, Ruben et al. have shown that the integral dose is in fact similar between 3D-CRT and IMRT [16]. Moreover, IMRT results in a smaller volume of pelvic marrow exposed to low dose radiation compared to 3D-CRT [17]. The superior dose conformity of IMRT also necessitates escalated treatment target alignment verifications, resulting in further increase in ionizing radiation exposure and increase in relative integral and peripheral dose unaccounted for in total dose calculation [18]. Despite the theoretical concerns about IMRT causing increased SM, a recent Surveillance, Epidemiology, and End Results (SEER) – Medicare linked study comparing SM after IMRT versus 3D-CRT concluded reduced risk for second colon and rectal cancer with IMRT [19].

Brachytherapy (BT) is another important RT modality. Compared to EBRT, BT delivers significantly higher dose to the prostate due to inherent dose inhomogeneity, and the dose decreases rapidly outside of the prostate resulting in less integral dose.

Because SM is rare and takes years to develop, studies often utilized the SEER database to ensure adequate statistical power. The common statistical method is standard incidence ratio (SIR) or Cox proportional hazards regression. However, both methods cannot account for all-cause mortality (ACM) as a competing risk for the development of SM. ACM is a far more likely outcome in

* Corresponding author at: Department of Radiation Oncology, Suite B265, 200 Medical Plaza, Los Angeles, CA 90095, United States.
E-mail address: chenyangwang@mednet.ucla.edu (C. Wang).

http://dx.doi.org/10.1016/j.radonc.2017.01.009
0167-8140/

cancer patients compared to SM, and it can exhibit significant bias across treatment cohorts. Without accounting for ACM as a competing risk, a high ACM may falsely inflate the risk of SM with either statistical approach.

In this study, we hypothesize that IMRT can result in a significant decrease in solid or hematologic SM risk due to the lower dose received by critical in-field organs such as the bladder, rectum and bone marrow. We propose to use the SEER database to investigate the differences in both solid and hematopoietic SM associated with radical prostatectomy (RP), EBRT and BT for clinically localized (cT1-2N0M0) PCa using a competing risk model described by Fine and Gray [20] to account for ACM and non-treatment related malignancies as competing risks for SM, while adjusting for age, year, T stage and Gleason score.

Materials and method

Patient population

This study was reviewed and approved by the institutional review board at our institution. We selected patients in SEER database with PCa diagnosed between January 1st, 1999 and December 31st, 2005 and underwent RP, EBRT or BT. The range of years was chosen to cover the transition from 3D-CRT to IMRT, with utilization of IMRT reaching an estimated 15.5% by 2002 [9]. For the year of diagnosis variable, years 1999–2001 are combined to represent patients treated predominantly with 3D-CRT, while years 2002–2005 are combined to represent patients treated with increasingly more IMRT. We excluded patients diagnosed in 2003 due to a change in Gleason score grouping, which prevented consistent grouping of the Gleason scores. We selected for patients with localized PCa (cT1-2N0M0) to minimize the likelihood of recurrence or metastases being mistaken for SM. Patients were excluded from further analysis if they: (1) were diagnosed via autopsy, (2) had non-adenocarcinoma histology, (3) were not in active follow-up, (4) had previous malignancy, (5) were younger than 18 years of age, or (6) received combined EBRT and BT. Hematopoietic SM have been shown to develop as early as two years after radiation exposure [21] while solid SM are thought to occur much later, compelling previous studies to use a threshold of five years [4,19,22–25]. We excluded patients whose time interval between PCa diagnosis and second malignancy or whose follow-up were less than five years and two years from solid and hematopoietic SM analyses respectively. Solid SM was defined as a single entity representing cancers arising from all critical in-field organs, including bladder cancer (superficial and muscle-invasive) and sigmoid/recto-sigmoid/rectal cancers. Hematopoietic SM included leukemia and lymphoma. Extracted variables included age, year of diagnosis, race, Gleason score, T stage, and treatment modality.

Statistical analysis

Analysis of variance (ANOVA) and chi-square tests were used to characterize differences in patient characteristics for continuous and categorical variables, respectively. Median follow-up was calculated via the reverse Kaplan–Meier method [26]. In order to account for ACM and non-treatment related malignancies as competing risks for SM, multivariate regression analyses based on the proportional hazards model described by Fine and Gray were applied to the data [20], while adjusting for age, year, treatment modality, T-stage and Gleason score. Patients who were alive at the last follow-up were censored. Subgroup analysis for SM stratified by definitive treatment modality was also carried out, and predicted cumulative incidence function (CIF) of solid or hematopoietic SM for each definitive treatment modality with respect to year was plotted using the respective competing risk models computed. All statistical analyses were carried out using R version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria) with 2-sided testing and a statistical significance threshold of 0.05.

Results

Patient characteristics for solid SM

The BT cohort had the fewest patients with Gleason 8–10 PCa (4.5%), whereas the EBRT cohort had the highest (18.0%), as shown in sTable 1 in Supplementary materials. The most common SM for all three definitive treatment modalities is bladder cancer, which occurred in 0.7%, 1.5% and 1.7% of patients treated with RP, EBRT and BT respectively. Patients in the EBRT cohort tend to be the oldest with a median age of 70 years, followed by 67 years for the BT cohort, and 61 years for the RP cohort. ACM is the highest for patients who underwent EBRT, constituting 24.1% of the cohort,

Table 1
Multivariate regression results for solid and hematopoietic SM, in the presence of non-treatment related malignancies and ACM as competing risks, according to the proportional hazards model described by Fine and Gray.

	Solid SM		Hematopoietic SM	
	AHR [95% CI]	*p*	AHR [95% CI]	*p*
Year				
1999–2001	1.000		1.000	
2002–2005	0.834 [0.754–0.922]	<0.001	0.829 [0.745–0.922]	0.001
Race				
Caucasians	1.000		1.000	
African American	0.699 [0.593–0.825]	<0.001	0.633 [0.526–0.762]	<0.001
Asian	0.717 [0.559–0.919]	0.009	0.815 [0.631–1.054]	0.120
Gleason				
5–7	1.000		1.000	
8–10	1.106 [0.963–1.27]	0.150	0.931 [0.796–1.089]	0.370
T stage				
T1	1.000		1.000	
T2	1.028 [0.932–1.134]	0.580	1.059 [0.952–1.179]	0.290
Treatment				
RP	1.000		1.000	
EBRT	1.931 [1.723–2.163]	<0.001	1.504 [1.335–1.693]	<0.001
BT	2.072 [1.822–2.355]	<0.001	1.214 [1.044–1.411]	0.012
Age at diagnosis	1.006 [1.004–1.008]	<0.001	1.005 [1.004–1.007]	<0.001

Please cite this article in press as: Wang C et al. Pattern of solid and hematopoietic second malignancy after local therapy for prostate cancer. Radiother Oncol (2017), http://dx.doi.org/10.1016/j.radonc.2017.01.009