RESEARCH ARTICLE

Secondary Malignancy after Treatment of Prostate Cancer. Radical Prostatectomy versus External Radiotherapy: A Retrospective Cohort Study

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ABSTRACT

Background: This study aims to determine whether the treatment of locally confined prostate cancer (PCa) with external radiotherapy (EBRT) increases the risk to develop secondary malignancies (SM) compared to radical prostatectomy (RPE). **Materials and Methods:** Data from patients who were treated curatively with RPE or EBRT from 2010 to 2018 and who did not have distant metastases, previous malignancy, or previous treatment with radiotherapy or chemotherapy at the time of diagnosis were reviewed to determine the incidence of SM over a median follow-up period of 47 months (range 12–96 months). Regression models were used to correlate the clinicopathological factors with the incidence of SM. **Results:** A total of 540 out of 1179 patients were eligible as per the study criteria. Of these, 316 patients underwent only RPE, while 224 patients received either definitive or adjuvant EBRT. Ten patients developed SM; 6 (1.9%) patients after RPE and 4 (1.8%) patients after EBRT. The sites of SM included stomach, bladder, rectum, lung, and palatoglossus. The median time to develop SM was 24 (9–40) and 58 (5–61) months after RPE and EBRT. Regression models showed no increase in the risk to develop SM after EBRT compared to RPE. However, patients with Grade 5 tumors harbored a higher risk to develop SM (hazard ratio 7.248, P = 0.002). **Conclusion:** At least in the observation period of this study, treatment of locally confined PCa with EBRT is not associated with a measurable increased risk to develop SM compared to RPE. Patients with high-grade PCa appear to be at more risk to develop SM.

Key words: Prostate cancer, radical prostatectomy, radiotherapy, secondary malignancy

INTRODUCTION

Both radical prostatectomy (RPE) and external radiotherapy (EBRT) are options for curative treatment of locally confined prostate cancer (PCa). The epidemiological data derived from atomic bomb survivors, nuclear accidents, as well as database analysis demonstrate a rare late effect of radiation to induce secondary malignancies (SMs).[1,2] Because PCa patients treated with curative intent now have improved survival, the ability to detect an increased risk of developing SM is enhanced.[3] Nevertheless, the current data on the incidence of SM after primary treatment of PCa with radiotherapy are still conflicting. While some studies suggest that radiotherapy is associated with increased risk of developing SM,[4-6] others have not confirmed this finding.[7-9] Furthermore, the available data on the incidence of SM after RPE are limited.

Intensity-modulated radiotherapy is a radiation technique that allows for dose escalation with the goal of reducing toxic side effects. Therefore, the risk of developing SM may be also different as compared to conventional techniques.[10]

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In this single-center cohort study, we compared the incidence of SM among PCa patients treated curatively with EBRT or RPE to determine whether radiotherapy either increased the risk of developing SM in this cohort or not. In daily clinical practice, this knowledge would be a helpful adjunct in patient counseling.

MATERIALS AND METHODS

The electronic medical records of patients who were treated in our PCa center between January 2010 and August 2018 were retrieved. A total of 1179 patients with PCa were registered. Only the patients with histologically confirmed PCa and who were primarily treated with curative intention using either RPE or with definitive or adjuvant EBRT and who were followed for at least 12 months were included in the study. Men with evidence of distant metastases at the time of diagnosis, a previous or synchronous malignant tumor, or those with a history of receiving chemotherapy or radiotherapy were excluded from the study. Patients who received salvage radiotherapy or chemotherapy due to biochemical failure were also excluded from further analysis beyond this point while patients who received adjuvant or concomitant androgen deprivation therapy (ADT) were not excluded from the study.

Using these criteria, a total of 540 patients were eligible to further statistical analysis. The medical records of these patients were reviewed for age at time of diagnosis, medical history, PSA values, Gleason score (in needle biopsy specimens), clinical staging, D'Amico risk stratification, type of treatment, total dose of radiotherapy, follow-up data, occurrence of biochemical failure, mortality and site, and time to develop SM.

This study was conducted retrospectively from data obtained for clinical purposes. An official waiver of ethical approval was granted from the institutional review board of our hospital.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, Armonk, NY, USA: IBM Corp.) for Windows version 23.0. Mean, median, and percentages were conducted to describe patients' characteristics. A Chi-squared test, *t*-test, and non-parametric test were used to test the statistical significance. Although a multivariate analysis was not possible because of the low number of SM cases observed ($n = 10$), a number of univariate regression models were used to analyze the data. $P \leq 0.05$ was considered to be statistically significant.

RESULTS

Medical records for 1179 patients with the diagnosis PCa were reviewed and the 540 of those that met the inclusion criteria were further divided into two groups according to the treatment received. The group treated with only RPE consisted of 316 patients (58.5%), whereas the group that received EBRT with curative intention consisted of 224 patients (41.5%). EBRT was indicated either as a definitive treatment in 152 patients (28.1%) or as an adjuvant therapy in 72 patients (13.3%) after RPE.

Table 1 shows a comparison of the characteristics of both groups of patients. Patients in the EBRT group had a higher median age (71.01 ± 7.4 years) than patients in the RPE group (67.21 ± 6.4 years). Furthermore, the patients that received EBRT had a higher incidence of lung and neurological diseases ($P = 0.004$ and 0.03, respectively). We noticed also that patients treated with EBRT had more unfavorable clinical and histopathological tumor features, that is, higher PSA, clinical stage, grade, and hence higher risk according to D'Amico classification. In a subanalysis, this tendency was maintained even when the patients treated with adjuvant EBRT were not included. This may explain why ADT was seen more frequently in patients that received EBRT than in patients treated with only RPE; 114 (50.9%) and 25 (7.9%) in EBRT and RPE patients, respectively ($P < 0.0001$). After a median follow-up of 47 months (range 12–96 months), there was no statistically significant difference in the incidence of biochemical failure between patients treated with only RPE and those treated with EBRT.

Table 2 shows that a total of 10 patients (1.85%) developed SM; 6 patients (1.9%) in the RPE group and 4 patients (1.8%) in the EBRT group. There was no statistically significant difference between the incidences of SM in both patients' groups ($P = 1.000$). The most frequent sites of SM was stomach, which was observed in 5 patients (50%); 2 and 3 patients in RPE und EBRT group. One of the patients who had stomach cancer after receiving EBRT developed SM 5 months, a local recurrence 8 months, and died of cancer 13 months after receiving the radiotherapy. Other origins for SM included bladder, rectum, lung and palatoglossus. Median time to develop SM was 24 months (range 9–40) in the RPE group and 58 months (range 5–61) in the EBRT group with no statistically significant difference ($P = 0.524$).

Table 3 demonstrates the results of a number of univariate regression models for occurrence of SM in total with age groups, T- and N-category, WHO grade, risk group, incidence of biochemical failure, primary treatment (only RPE vs. EBRT), use of adjuvant or concomitant ADT, and dose of radiotherapy as influencing factors. Only Grade 5 tumor was a predictor for the development of SM (hazard ratio 7.248; $P = 0.002$). In this analysis, treatment with EBRT was not a predictor for the development of SM compared to only RPE.

DISCUSSION

RPE and EBRT are curative treatment options for locally confined PCa and the literature still shows conflicting and controversial results;[11] some studies report that EBRT

Table 1: Patient characteristics

	RPE only *n*=316/540 (100%)	ERBT (definitive or adjuvant) *n*=224/540 (100%)	*P*-value*
Age			
Age years (Mean±SD)	67.21±6.4	71.01±7.4	<0.0001
≤65 years	113 (35.8)	46 (20.5)	<0.0001
66–75 years	166 (52.5)	100 (44.6)	
≥ 76 years	37 (11.7)	78 (34.8)	
Medical history			
Cardiovascular disease	122 (38.6)	101 (45.1)	0.132
Diabetes mellitus	26 (8.2)	26 (11.6)	0.190
Lung disease	5 (1.6)	14 (6.3)	0.004
Musculoskeletal disease	19 (6)	22 (9.8)	0.100
Thyroid disease	7 (2.2)	3 (1.3)	0.534
Renal disease	7 (2.2)	7 (3.1)	0.512
Gastrointestinal disease	13 (4.1)	9 (4.0)	0.956
Neurological disease	10 (3.2)	16 (7.1)	0.033
Psychological disorder	3 (0.9)	7 (3.1)	0.102
Character of the tumor (cT)			
cT1	197 (62.3)	143 (63.8)	<0.0001
cT2	119 (37.7)	65 (29.0)	
cT3	0 (0.0)	15 (6.7)	
cT4	0 (0.0)	1 (0.4)	
cN			
cN –ve	316 (100)	220 (98.2)	0.029
cN +ve	0 (0.0)	4 (1.8)	
Gleason score (biopsy)			
Grade 1	91 (28.8)	31 (13.8)	<0.0001
Grade 2	116 36.7)	62 (27.7)	
Grade 3	44 (13.9)	40 (17.9)	
Grade 4	45 (14.2)	50 (22.3)	
Grade 5	20 (6.3)	41 (18.3)	
PSA (ng/ml) median (range)	7.22 (1.2–117)	9.55 (0.45–181.68)	<0.0001
Risk stratification			
Low risk	65 (20.6)	18 (8.0)	<0.0001
Intermediate risk	135 (42.7)	90 (40.2)	
High risk	116 (36.7)	116 (51.8)	
Hormonal treatment	25 (7.9)	114 (50.9)	<0.0001
PSA failure**	42 (13.3)	34 (15.2)	0.534
Localization of the recurrence/metastases* **	***n*=42 (100%)**	***n*=34 (100%)**	
Biochemical failure without localization	32 (76.2)	16 (47.1)	
Regional lymph nodes	7 (16.7)	9 (26.8)	
Bone metastases	3 (7.1)	9 (26.8)	
Lung metastases	0 (0.0)	4 (11.8)	
Brain metastases	0 (0.0)	1 (2.9)	
Local recurrence	0 (0.0)	2 (5.9)	
Adrenal gland	0 (0.0)	1 (2.9)	
Non-regional lymph nodes	1 (2.3)	1 (2.9)	
Death**	5 (1.6)	14 (6.3)	0.003

**P*-value ≤0.05 significant. **Median follow-up 47 months (range 12–96 months). ***Many patients have more than 1 site for recurrence/metastases

Table 2: Incidence and sites of SM

	RPE only *n*=316/540 (100%)	ERBT (definitive or adjuvant) *n*=224/540 (100%)	*P*-value*
SM**	6 (1.9%)	4 (1.8%)	1.000
Bladder	1	1	
Stomach	2	3	
Lung	1	0	
Rectum	1	0	
Palatoglossus	1	0	
Time to occurrence of SM median (range)	24 (9–40) months	58 (5–61) months	0.524

*P-value ≤0.05 significant. **Median follow-up 47 months (range 12–96 months)

Table 3: Hazard ratio with 95% confidence interval for SM according to age group, cT and cN stage, WHO grade, risk stratification, received treatment (RPE, ERBT, and ADT), dose of radiotherapy, and incidence of biochemical failure

Patients: *n*=540 events: *n*=10

Covariates	Hazard ratio	95% confidence interval		*P*-value*
Age groups				
≤65 years	1.577	0.445	5.588	0.481
66–75 years	0.682	0.193	2.418	0.554
≥76 years	0.948	0.201	4.467	0.946
Clinical stage				
cT1	0.520	0.138	1.952	0.332
cT2	1.318	0.324	5.358	0.700
cT3	6.541	0.816	52.441	0.077
cT4	0.050	0.00	1.523	0.946
cN				
cN +ve	0.049	0.0	3.985	0.872
WHO grade (needle biopsy)				
G1	0.031	0.0	13.671	0.264
G2	1.259	0.355	4.464	0.721
G3	0.597	0.076	4.716	0.625
G4	0.586	0.074	4.635	0.613
G5	7.248	2.028	25.899	0.002
Risk stratification				
Low risk	0.038	0.0	51.439	0.373
Intermediate risk	0.763	0.214	2.717	0.676
High risk	2.617	0.730	9.380	0.140
Treatment group (RPE vs. EBRT)	0.896	0.252	3.181	0.865
Treatment with ADT	1.616	0.415	6.302	0.489
Doses of radiotherapy (<70 Gy vs. ≥70 Gy)	0.626	0.065	6.020	0.685
Biochemical failure	1.321	0.280	6.231	0.725

*P≤0.05 significant

treatment is associated with increased risk of developing SM,[4-6] whereas others did not find such an association.[7-9] The exact pathogenesis of radiation-induced malignancies still not clear and the histopathological features of these malignancies could not be differentiated from similar origin malignancies in non-irradiated patients.[12]

A literature review by Murray *et al*. highlighted the difficulty in associating radiotherapy with increased risk of developing SM in PCa patients although they observed a small increase in the risk in several studies.[2] In a recent meta-analysis, Zhao *et al*. also reported an increased risk of developing bladder cancer after radiotherapy for PCa although absolute effect was low and the results were inconsistent in the subanalysis over the different follow-up periods.[13]

In our retrospective cohort analysis, we compared the incidence of SM after curative treatment of locally confined PCa in patients treated with EBRT (definitive or adjuvant) in comparison with only RPE as a control group. We did not find a statistically significant difference in the incidence of SM between the irradiated (1.8%) and non-irradiated patients (1.9%) (P = 1.000). As a matter of fact, because one of the patients developed stomach cancer only 5 months after EBRT, a correlation between the EBRT and the appearance of stomach cancer in this patient would be unlikely. Analysis of the data using regression models also failed to uncover a correlation between the treatment of PCa with EBRT and the development of SM compared to treatment with RPE (RPE compared to EBRT: Hazard ratio 0.896; P = 0.865). On the other hand, diagnosis of a Grade 5 tumor was a predictor for the development of SM (hazard ratio 7.248; P = 0.002). This raises the question of whether a correlation might exist between PCa and the susceptibility for the development of other site primary malignancies. Indeed, Ko *et al*. reported that the risk of advanced colorectal neoplasms is significantly increased in PCa patients and recommended that PCa patients have a colonoscopy at the time of diagnosis of PCa.[14] Van Hemelrijck *et al*. also reported that PCa patients were at higher risk of developing secondary primary cancers irrespective of the treatment modality and suggested that increased diagnostic attention may explain an increased incidence of SM, especially in the first few years after PCa diagnosis.[15]

Wallner *et al*. found that ADT was not associated with increased risk of developing SM in a large population-based study of 24,038 patients with localized PCa. Interestingly, radiotherapy did not modify the association between the ADT and the development of SM.[16] In our cohort, ADT was observed more frequently in patients that received EBRT and these patients had more unfavorable clinical and pathological tumor features. The regression models did not detect a statistically significant increase in the risk to develop SM in patients that received ADT compared to patients that did not (hazard ratio 1.616; P = 0.489).

The most common pelvic and potential sites of SM after radiotherapy treatment of PCa were bladder, sigmoid colon, rectum, non-Hodgkin lymphoma, multiple myeloma, chronic lymphocytic leukemia, and acute myeloid leukemia as well as sites in the upper body that were unlikely related to radiotherapy such as esophagus, stomach, cecum, ascending colon, transverse colon, lung and bronchus, kidney, renal pelvis, pancreas, larynx, brain, and skin melanoma.[3,7] SM originated in our cohort from stomach, bladder, rectum, lung, and palatoglossus. It is worthy to note that the most common site to develop SM in our cohort was the stomach with total of five patients from both groups (50% of SM cases) having developed stomach cancer. None of these patients had relevant medical history for the development of stomach cancer such as chronic gastritis, infection with *Helicobacter pylori*, stomach polyps, or pernicious anemia.[17] However, data about smoking and other related lifestyle habits were deficient.

In a study that included 6091 patients, Kutikov *et al*. reported that patients treated with radiotherapy were typically older, harbored more comorbidities, and had more unfavorable pathologic tumor features than patients undergoing RPE.[18] Such a finding was also reported by Hegemann *et al*. in another larger population study of 19,538 patients.[7] In a recent interesting analysis of 2373 patients, Milonas *et al*. investigated the age-related specific characteristics of PCa patients after RPE and they found that patients older than 65 years had a 1.5-fold increased risk of having high-risk PCa compared to younger patients.[19] This is consistent with our results that the patients treated in the EBRT group had a higher median age, a greater incidence of lung and neurological diseases, higher PSA, clinical stage, grade, and higher risk according to D'Amico risk stratification.

In a review of the epidemiologic studies of the radiation dose–response relationship, de Gonzalez *et al*. reported that the relative risk of developing SM is 5–10 times higher at 40 Gy compared to non-irradiated patients or patients who received low doses. However, there was no evident nonlinearity in the direction of risk reduction at doses of 60 Gy or higher when all second cancer sites were considered.[20] The patients receiving EBRT treatment in our cohort were separated into two groups according to the total dose of radiation received. The patients who had definitive radiotherapy received ≥70 Gy (70–78 Gy); meanwhile, the patients who had adjuvant radiotherapy received doses <70 Gy (64–68 Gy). The regression models showed that the dose of radiotherapy was not a predictor for the development of SM in the radiated patients.

Zhao *et al*.[13] conducted a meta-analysis of a total of 15 studies with heterogeneous populations; they reported that previously the lag time between radiotherapy and developing a SM was 5 years. In their meta-analysis, only four included studies provided the follow-up data of the patients for more than 5 years. The results were inconsistent; two studies failed to demonstrate a correlation between radiotherapy and developing bladder cancer and the other two studies demonstrated such a correlation. The follow-up period in

our cohort ranged from 12 to 96 months with a median of 47 months. The median time to develop SM in RPE and EBRT groups were 24 (9–40) months and 58 (5–61) months, respectively (P = 0.524). The patients treated with EBRT were older (median age 71.01 ± 7.4 years) and harbored more comorbidities than those treated with RPE. Hence, the significance of extending the observation period more than 10 years may be debatable due to probably shorter life expectancy of these patients.

This study has a number of limitations including the limited power due to the relatively small number of patients that developed SM and also the missing data regarding smoking and other lifestyle factors that might compound cancer risk. In addition, because the follow-up period ranged from 12 to 96 month, this led to a shorter observation period in some patients. However, this study represents a single-center database analysis of a homogenous population of patients. The techniques, that is, radiotherapy techniques and surgical approaches, were the same in both groups over the study period. Furthermore, this analysis investigated the carcinogenic effect of EBRT compared to RPE as a control group and raised again the question of whether a correlation between PCa and the development of SM might be inherited. Further, in-depth investigations of the tumor biology of both PCa and SM are required to truly test such a hypothesis.

CONCLUSION

Our results suggest, at least in the observation period of this study, that the treatment of locally confined PCa with EBRT may not be associated with a measurable increased risk of developing SM compared to RPE. High-grade PCa may be associated with such an increased risk. We recommend further prospective studies to clarify the biological link between PCa and the SM.

AUTHORS' CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Mohammed Hassan. The first draft of the manuscript was written by Mohammed Hassan and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript for submission.

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