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Original Article

Second primary malignancy after radical prostatectomy in a cohort from Middle East

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ABSTRACT

Background: Our objective was to estimate the overall risk of developing second primary malignancy (SPM) among Middle Eastern men with prostate cancer who underwent surgical extirpation of their prostate.

Materials and methods: We conducted a retrospective study of 406 patients who underwent radical prostatectomy in a tertiary centre and who had no evidence of previous malignancy from 1998 to 2012. Standardized incidence ratios (SIRs) and 95% confidence interval (CI) were calculated to analyze the risk of SPM in our population compared with the general population. Cox-regression models were also conducted to correlate the clinicopathological factors with the development of SPM.

Results: After 14 years of follow-up, the incidence rate of SPM was 100.9 per 1,000 person-years. The most frequent SPMs were bladder cancer ($n = 11$, 27%) followed by hematological malignancies ($n = 9$, 22%) and lung cancer ($n = 7$, 17%). The overall risk for men with prostate cancer to develop SPM is lower than the men in the general population (SIR = 0.19; 95% CI: 0.14–0.25). A multivariate analysis failed to correlate any of the clinicopathological factors with the development of SPM.

Conclusion: Patients with prostate cancer who underwent surgical expiration of their prostate are at lower risk of developing SPM compared with the general population.

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1. Introduction

Prostate cancer is the second most common malignancy diagnosed in men and the fifth leading cause of cancer-related death worldwide.[1] The mortality rates are decreasing after the adoption of prostate cancer screening, along with the refinement of treatment modalities for local disease.[2] Improved prostate cancer survival is leading to longer follow-up and might contribute to an apparent increased risk of second primary malignancies. Following radical treatment of localized prostate cancer, men are followed-up by their urologist or oncologist with regular prostate-specific antigen (PSA) testing. This regular follow-up is also an opportunity to reinforce health promotion messages and cancer prevention strategies.

In a recent analysis of the United States Surveillance, Epidemiology, and End Results (US SEER) data, the incidence of second primary malignancy (SPM) was 15.2% at 25 years for all cancers.[3] Increased risk of SPM is known to be associated with exposure to radiotherapy and chemotherapy.[4] Nevertheless, other factors can contribute to developing SPM such as genetic predisposition and exposure to carcinogens. Davis et al[5] evaluated the risk of SPM using SEER data after treatment of prostate cancer and concluded that prostate cancer survivors had a lower risk of being diagnosed with another cancer compared with the rest of the US population; however, racial differences were observed, and men treated with external-beam radiation therapy had small long-term increases in their risk of bladder and rectal cancer.

Data regarding the risk of SPM after radical prostatectomy are limited, and no data are available for the Middle Eastern population who are known to have high rates of smoking and a high incidence of bladder cancer.[6]

In this study, we aimed to estimate the overall risk of developing SPM among Middle Eastern men with prostate cancer who underwent surgical extirpation of their prostate.

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2. Materials and methods

The Institutional Review Board at our institution approved the study. We conducted a retrospective study of 406 patients who underwent radical prostatectomy in a tertiary centre in Lebanon and who had no evidence of previous malignancy from 1998 to 2012. Patients' medical records were reviewed and included age, PSA values, time to develop SPM, pathology results, and adjuvant treatment. The origin and type of SPM were also documented. The data were evaluated for the incidence of developing a second primary malignancy.

2.1. Statistical analyses

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows version 22.0. Median and percentages were conducted to describe patients' characteristics. To analyze the relative risk of SPM in our Lebanese population compared with general populations, we calculated standardized incidence ratios (SIRs) and their 95% confidence interval (CI). SIR is the ratio obtained by dividing the number of observed second cancer cases by the number of expected cases.

Cox regressions models were conducted to correlate the clinicopathological factors with the development of SPM. Multivariate analyses were adjusted for age, radiation therapy, biochemical recurrence, Gleason score, extraprostatic extension, surgical margin, and seminal vesicle invasion. All P values ≤ 0.05 were considered to be statistically significant.

3. Results

The median age and follow-up of the cohort were 62 years and 108.9 months respectively (Table 1). After 14 years of follow-up, the incidence rate of SPM was 100.9 per 1,000 person-years (41 new cases). The most frequent SPMs were bladder cancer ($n = 11$, 27%) followed by hematological malignancies ($n = 9$, 22%) and lung cancer ($n = 7$, 17%). Taking the population study ($n = 406$), the incidences for this cohort were 2.7% bladder cancer, 2.2% lymphoma, and 1.7% lung cancer.

Table 1
Characteristics of the prostate cancer patients underwent RP, 1998–2012

	Total
	$n = 406$ (%)
Median age, y	62
Median PSA	6.9
Median follow-up, mo	108.9
Adjuvant radiation therapy	142 (35)
SPM patients	
$n = 41$	
Median age at diagnosis, y	66
Median preoperative PSA	4.62
PSA failure	11 (27)
Pathologic stage	
T2	27 (66)
T3	14 (34)
Gleason score	
6	15 (37)
3 + 4	19 (46)
> 8	7 (17)
D'amico characteristics	
Low risk	14 (34%)
Intermediate risk	16 (39%)
High risk	11 (27%)
Adjuvant radiation therapy	12 (29)

PSA, prostate-specific antigen; RP, ; SPM, second primary malignancy.

When compared with the incidence rates of cancer in the Lebanese men, the overall risk for men with prostate cancer to develop SPM is lower than the men in the general population (SIR = 0.19; 95% CI: 0.14–0.25).[6] The reduction in risk was significant for all solid tumors including bladder cancer (Table 2). A multivariate analysis failed to correlate any of the clinic-pathological factors with the development of SPM (Table 3).

The effect of radiation therapy was studied. A group of 29% of our patients ($n = 117$) underwent adjuvant radiation therapy (ART). Five patients developed bladder cancer, corresponding to 4.3% incidence in this cohort, two developed lymphoma and leukemia (1.7%), and one patient developed lung cancer (0.9%).

Although there was a trend towards a higher incidence of bladder cancer in patients receiving ART 4.3% compared with 2% (6/289) the difference was not statistically significant.

3.1. Latency

The median time to diagnose SPM in all patients was 87.8 months. The median time from diagnosis of SPM to the last follow-up was 29.5 months. The median time to diagnose bladder cancer after radical prostatectomy was 52.5 months. There was no difference in the median time to develop bladder cancer between patients who received ART and those who did not.

4. Discussion

Our study showed that the incidence rate of SPM after undergoing surgery as the initial treatment of prostate cancer is lower than the rate observed in the Lebanese general population.[6] Moreover, the observed rate of developing SPM in our cohort (SIR = 0.19; 95% CI: 0.14–0.25) is lower than the rate reported in previous studies.[5,7]

This variation in the rate of SPM among different studies arises from the difference in the follow-up period, racial background, and type of registry used for analysis. Moreover, none of these studies looked into the environmental and lifestyle factors, nor did they address the associated comorbidities.

The most frequent second primary malignancies observed in our study, respectively, were bladder cancer, lymphoma and leukemia, and lung cancer. However, the most commonly reported malignancies in the Lebanese men in 2008 were lung, bladder, and prostate cancer, respectively.[6] The increased risk of bladder cancer in our cohort can be attributed to vigilant follow-up of patients after surgery by urologists, and probably in some patients to the effect of radiation therapy although this has not been proven statistically.

Radiotherapy has been associated with increased risk of developing a secondary malignancy.[8–10] Based on the organ equivalent doses model which is used to describe radiation-induced cancer after radiotherapy (OEDrad-ther) in the irradiated organs; de Gonzalez et al has demonstrated that second cancers after radiation therapy arise in areas which received > 5 Gy.[11] Interestingly, dose–risk relationship for second rectal and bladder cancer plateaus between 1 Gy and 60 Gy.[12] However, a few studies illustrate that bladder cancer incidence in patients with prostate cancer treated with surgery is similar to that of the general population, even for those who received adjuvant radiation.[13–15]

A patient's age at diagnosis and treatment of prostate cancer can also be a predictor for developing SPM. Research on survivors of Hodgkin lymphoma and testicular cancer found that when compared with the general population, the relative risk of developing SPM is higher at younger versus older ages.[16] In addition, the baseline cancer rates in the general population are higher in elderly people, the cumulative exposure to carcinogens (which may

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