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Original Article

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

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ABSTRACT

Background: Data from the Middle East regarding second primary malignancy (SPM) after radical prostatectomy are limited. 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 (standardized incidence ratios = 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.

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, Armonk, NY, USA: IBM Corp.) 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 of the cohort was 62 years, median follow-up was 108.9 months (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, Radical prostatectomy; 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 after the diagnosis of prostate cancer. 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, increase

Table 2
Standardized incidence ratio of patients with prostate cancer

SPM types	Cases *n* (%)	Incidence	ASR[a)] (%)	SIR	SIR Davis et al[5, b)]	SIR Joung et al[7, b)]
All sites	41 (100)	100.9[c)]	225.7	0.19 (0.14–0.25)	0.55 (0.53–0.56)	0.78 (0.72–0.78)
Bladder cancer	11 (27)	2.7%	34	0.33 (0.17–0.56)	0.76 (0.70–0.83)	1.55 (1.09–1.45)
Lymphoma & leukemia	9 (22)	2.2%	4.2	0.64 (0.31–1.17)	0.84 (0.74–0.94)	0.9 (0.69–1.03)
Lung cancer	7 (17)	1.7%	31.8	0.22 (0.10–0.44)	0.68 (0.63–0.73)	0.67 (0.59–0.7)

ASR, age standardized ratio; SIR, standardized incidence ratio; SPM, second primary malignancy.
[a)] ASR for Lebanese men based on 2008 figures.
[b)] Incidence of SPM in prostate cancer patients who underwent surgical treatment.
[c)] Incidence ratio per 1,000 person-years.

Table 3
Hazard ratio (HR) with 95% CI for secondary primary malignancies according to radiotherapy, PSA, and Gleason score in the cohort study, 1998–2012

Total number of cases		SPM patients	
		Age-adjusted HR	Multivariate-adjusted HR
Radiation therapy			
No	27	1.00	1.00
Yes	12	0.36 (0.10–1.29)	0.18 (0.03–1.21)
PSA fail			
No	30	1.00	1.00
Yes	11	1.38 (0.35–5.45)	0.42 (0.06–3.07)
Gleason score			
6	15	1.00	1.00
7	19	1.14 (0.22–5.82)	0.76 (0.06–9.40)
8	7	1.44 (0.30–6.94)	1.14 (0.14–9.36)
Extra prostatic extension			
No	27	1.00	1.00
Yes	14	0.86 (0.31–2.44)	1.17 (0.12–11.64)
Surgical margin			
No	20	1.00	1.00
Yes	21	0.77 (0.26–2.30)	0.41 (0.06–3.02)
Seminal vesicle invasion			
No	34	1.00	1.00
Yes	7	1.12 (0.32–3.95)	4.51 (0.26–78.69)

Adjusted model for age (y), radiation therapy (yes/no), PSA failure (yes/no), Gleason score (6, 7, and > 8), extra prostatic extension (yes/no), surgical margin (yes/no), and seminal vesicle invasion (yes/no).
CI, confidence interval; HR, hazard ratio; PSA, prostate-specific antigen; SPM, second primary malignancy.

mutational load and immunosenescence.[17] These findings highlight the importance of age at initial treatment and attained age (age at SPM occurrence) as a determinant of treatment-related SPM risks. In our study, 56% of patients who developed hematological malignancy were older than 70 years at the time of prostate cancer diagnosis.

Our findings raise the question of the need for screening for SPMs on follow-up visits. Research on the screening of cancer survivors has mainly focused on breast cancer after Hodgkin lymphoma.[1,18–20] Amid the absence of recommendations on the screening of prostate cancer survivors, and bearing in mind the low relative risk of developing SPM in our population, the need to do systematic screening is questionable. In our cohort, all the patients who developed lung cancer as SPM were smokers or ex-smokers, adding to the high age standardized ratio (ASR, 31.2) of lung cancer observed. We are advocates for US Preventive Services Task Force lung cancer screening recommendation in patients who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years to have an annual low-dose computed tomography scan.[21]

The value of bladder cancer screening in the general population has been perplexing the uro-oncology community for the past decade. Up to now, there is no recommendation for bladder cancer screening in the general population. Bladder cancer screening studies were performed in countries with low incidence of bladder cancer, and this may play a significant role in disparaging the value of bladder cancer screening programs.[22] However, there is compelling evidence of the benefit of bladder cancer screening in highly selected patients.[23]

In light of the absence of reliable biomarkers to identify patients at risk; cystoscopy should be considered in high-risk patients i.e., those patients who have a history of smoking > 40 pack/year, microscopic hematuria, and exposure to petroleum and dyes and radiation therapy.[22]

Our study has the limitations of being retrospective and having a relatively small sample size; however, most patients had a long-term follow-up at our institution.

Patients with prostate cancer who underwent surgical extirpation of their prostate are at lower risk of developing SPM compared with the general population. Urologists should take into consideration individual risk factors to counsel their patients for screening for SPM during their follow-up after prostate cancer treatment. The role of additional risk factors related to genetic predisposition or treatment effect (radiation therapy) needs further evaluation.

Conflicts of interest

Nothing to disclose. No financial support was received for this study.

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