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Impact of body mass index on clinico-pathological parameters and outcome in patients with metastatic prostate cancer

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KEYWORDS

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Abstract *Background:* This study evaluates the correlation between body mass index (BMI) and clinicopathological parameters of metastatic prostate cancer (MPC) and its impact on survival.
Method: During the study period, 71 MPC patients were eligible. Patients with BMI $< 25.0\ kg/m^2$ were categorized as level I and patients with BMI $\geqslant 25.0\ kg/m^2$ were categorized as level II. Demographic features and survival rates were evaluated by the Kaplan–Meier method and Cox proportional models.
Results: 31 patients belonged to level I while the rest belonged to level II with insignificant higher median follow-up duration in level II; $p = 0.5$. In terms of age, metastasis, serum level of albumin, prostatic specific antigen, alkaline phosphatase (AKP) and Gleason score, there was no significant difference between the two levels. The cumulative survival probability in the 12th, 24th and 36th month in level I vs; level II was; 86.7%, 68.7%, 64.1% vs; 74.4%, 67.7%, 55.1%, respectively with 7 patients dead in level I compared to 14 patients dead in level II denoting a higher PC-specific death rate in the level II group.
In univariate and multivariate analysis, poor prognosis was associated with increasing AKP (HR = 1.0005, 95% CI, $p = 0.03$; HR = 1.001, 95% CI, $p = 0.03$) respectively, while better prognosis was associated with no visceral metastasis (HR = 0.09, 95% CI, $p = 0.000$; HR = 0.04, 95% CI, $p = 0.000$) and increasing albumin levels (HR = 0.17, 95% CI, $p = 0.000$;

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HR = 0.15, 95% CI, $p = 0.000$) respectively. In multivariate analysis only, patients belonging to level I were associated with better prognosis (HR = 0.17, 95% CI, $p = 0.02$).
Conclusion: BMI is dependent on prognostic factors in patients with MPC.

Introduction

Prostate cancer (PC) has surpassed lung cancer as the most commonly diagnosed cancer in men. An estimated 230,000 new cases were diagnosed in 2014, accounting for 27% of new cancer cases in men [1].

Although 80–90% of PC with metastatic lesions responds to initial androgen ablation therapy, most of these patients ultimately develop progressive disease of hormone refractory cancer [2].

Obesity, as a growing epidemic all over the world, has been linked to mortality of several cancers [3]. Only in the past 5 to 10 years, BMI as a surrogate of adiposity has been evaluated for PC incidence, but the relation between BMI and aggressive PC is still not fully evaluated [4].

An epidemiologic study reported that obesity may be protective against the development of early stage PC. On the contrary, other studies have shown that obesity may be associated with an increased risk of advanced disease and death from PC [5].

Amling et al. reported higher rates of positive surgical resection margins and biochemical recurrence in obese patients with localized PC undergoing radical prostatectomy than in normal-weight patients, which are considered to be a representative example of an association between obesity and localized PC [6].

To our knowledge, studies are still lacking on the relation between BMI and metastatic prostate cancer (MPC).

The aim of the current study is to assess the relation between BMI, clinicopathological parameters and the outcome of MPC.

Materials and methods

The current retrospective cohort design included 71 MPC patients during the period from January 2011 to March 2015 who were diagnosed and treated in King Abdullah Medical City (KAMC) and 7 were excluded due to incomplete data. The eligibility criteria were; histological confirmed PC, evidence of metastatic disease, by use of the medical records of the patients, the demographic data including age at time of diagnosis, pathological features, serum prostatic specific antigen (PSA) level, Gleason score, serum AKP, serum LDH, complete blood count, liver profile, renal profile, metastasis to the internal organs, and follow-up period were investigated retrospectively. BMI was calculated at the time of diagnosis, we used measured weight and height to calculate BMI (kg/m^2). According to the World Health Organization Guidelines, Patients were classified into 2 levels: patients with BMI ($<25\ kg/m^2$) were categorized as level I and patients with BMI ($\geqslant 25\ kg/m^2$) were categorized as level II. Clinicopathologic and outcome data were tested for its relation with BMI.

Statistical analysis

Data were analyzed by using SPSS version 17 (SPSS Inc., Chicago, IL, USA) and has been subjected to descriptive analysis. The variables like subjects; visceral metastasis, lymph node involvement, bone metastasis, life status, and BMI, i.e., (<25 and $\geqslant 25$) were taken as binary nominal variables. On the other hand, age, serum levels of; prostatic specific antigen PSA, AKP, lactate LDH and duration in months from the start of treatment to death or last follow up were taken as continuous variables. Categorical variables have been expressed as *n* (%), undergone cross tabulation and compared by Chi-square or Fisher exact test where appropriate. Continuous data were subjected to normality testing by the Shapiro–Wilk test and expressed as mean ± standard deviation (SD) or median (minimum–maximum). Continuous data were compared by using Student's *t* test or Mann Whitney U test after determining the normality. Time to death was assessed using survival analysis (Kaplan–Meier curve) and the differences in survival distributions for BMI categories were evaluated via Log Rank (Mantel-Cox) test. Moreover, the analysis is further supported by mean survival time with 95% confidence interval along with cumulative survival probability at different points in time. Univariate as well as multivariate Cox proportional hazards model has been used to estimate hazard ratios (HRs) and 95% confidence interval for deaths due to metastatic prostate cancer from all predictors by using the time duration in months since the treatment started. An alpha level of <0.05 has been considered significant for each analysis.

Results

A total of 71 patients were included in the study, according to subjects' BMI level, 31 patients (43.7%) belonged to level I while the rest belonged to level II. Though median follow up duration appeared to be longer in level II BMI, than level I yet not significant, 20.4 (0.1–44.1) months vs; 14.3 (2.1–36.6) months respectively, $p = 0.5$. In addition, there were no significant differences between the two levels in terms of age, visceral metastasis, bone metastasis, serum levels of albumin, PSA, AKP and degree of differentiation (Gleason score). However, serum LDH levels were significantly higher in level II subjects than the level I group, i.e., median (range) 212 (47–1937) than 163 (65–4575), $p = 000$, respectively (Table 1).

The cumulative survival probabilities in 12th, 24th and 36th month of the level I and level II groups were; 86.7%, 68.7%, 64.1% and 74.4%, 67.7%, 55.1%, respectively. In the level I group, 7 patients died of PC, while in the level II group, 14

Table 1 Patients' characteristics according to BMI.

Parameters	Body mass index (kg/m^2)		*N*	*p*-Value
	Level I	Level II		
Patients numbers (%)	31 (43.7%)	40 (56.3%)	71 (100%)	0.3
Age (years)	72.2 ± 9.1	71.9 ± 8.6	72 ± 8.7	0.8
Poorly differentiated Pathology (Gleason score 8–10) (yes)	10 (32.3%)	15 (37.5%)	25 (35.2%)	0.6
Visceral metastasis (yes)	6 (19.4%)	12 (30%)	18 (25.4%)	0.3
Bone metastasis (yes)	23 (74.2%)	35 (87.5%)	58 (81.7%)	0.2
Prostatic specific antigen	39 (1–2715)	66.3 (0.1–16,430)	54 (0.1–16,430)	0.7
Albumin	3.2 ± 0.5	3.3 ± 0.7	3.2 ± 0.6	0.7
Lactate dehydrogenase (U/L)	163 (65–4575)	212 (47–1937)	187 (47–4575)	0.00
Alkaline phosphatase (U/I)	103 (42–4940)	109.5 (48–3280)	107 (42–4940)	0.6
Follow up (months)	14.3 (2.1–36.6)	20.4 (0.1–44.1)	14.4 (0.1–44.1)	0.7

patients died of PC, thus showing a higher PC-specific death rate in the level II group than the level I group (Fig. 1).

In the Univariate Cox-proportional hazard model, poor prognosis was associated with increasing serum AKP (HR = 1.0005, 95% CI 1.0005–1.001, $p = 0.03$) and serum LDL (1.001, 95% CI 1.0002–1.001, $p = 0.01$) levels while better prognosis was associated with no visceral metastasis (HR = 0.09, 95% CI 0.03–0.2, $p = 0.000$) and increasing serum albumin level (HR = 0.17, 95% CI 0.09–0.34, $p = 0.000$) (Table 2).

In the Multivariate Cox-proportional hazard model, poor prognosis was associated with increasing serum AKP level (HR = 1.001, 95% CI 1.0001–1.002, $p = 0.03$) while better prognosis was associated with no visceral metastasis (HR = 0.04, 95% CI 0.008–0.2, $p = 0.000$), increasing serum albumin level (HR = 0.15, 95% CI 0.05–0.4, $p = 0.000$) and BMI < 25 (HR = 0.17, 95% CI 0.04–0.7, $p = 0.02$).

Discussion

Obesity is a major health problem throughout the world, which has been linked to the development of various malignant diseases, including colorectal cancer, breast cancer and PC [7]. Conversely, the relationship between PC and obesity is still a matter of debate [8].

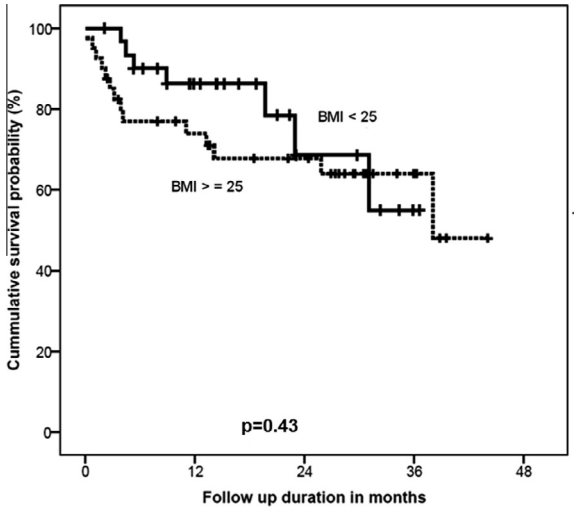

Figure 1 Kaplan–Meier survival curves demonstrating patients' cancer-specific survival for metastatic prostate cancer on the basis of body mass index. BMI, body mass index.

The findings reported in the present study that provide better prognosis were associated with BMI < 25 kg/m^2. In the multivariate analysis, serum AKP levels, serum albumin levels, visceral metastasis, and BMI < 25 kg/m^2 were reported as significant prognostic factors with cumulative survival probability in 10, 20 and 30 months favoring low BMI < 25 kg/m^2.

These results are consistent with many previous studies. Rodriguez et al. [9] found PC mortality rates to be significantly higher among obese men.

Efstathiou et al. [10] reported greater baseline BMI is independently associated with higher PC-specific mortality in men with locally advanced PC. According to Gong et al. [11], obesity at the time of diagnosis was associated with increased risks of PC metastasis and death. In a prospective cohort study on 5313 men who underwent radical prostatectomy, Siddiqui et al. [12] demonstrated worse clinical and pathologic features in patients with a higher BMI. There are additional studies concluding the same results [13–16].

On the other hand, our results contradict some studies that reported better effects of obesity on PC. A retrospective study was conducted of 55 patients who were diagnosed with castration-resistant prostate cancer (CRPC) and received docetaxel treatment between 2003 and 2009. The findings suggested that BMI as well as other prognostic factors are independent prognostic factors in patients with CRPC who receive docetaxel treatment, with improvement in cancer specific survival rate in patients with high BMI [17]. In another study Strom et al validated the importance of obesity in PC progression and biochemical failure in patients treated with external beam radiotherapy [18].

Moreover, a similar result was reported by Halabi et al. [19] of a total of 1,226 patients with CRPC, the overall survival rate and cancer-specific survival rate of overweight and obese patients were higher than those of the normal-weight patients.

Several possible explanations have been proposed to clarify the correlation between PC and obesity, hormonal and metabolic changes are the primary concern. First is that certain obesity-related metabolic dysregulation such as hyperinsulinemia and/or hypoadiponectinemia favors aggressive neoplastic behavior [20,21].

Second is the association between lower levels of testosterone in obese men and the poorly differentiated and hormone insensitive tumors [22,23].

Table 2 Factors affecting cancer-specific survival in patients with MPC; Multivariate and univariate analyses.

		Multivariate Cox regression hazard model				Univariate Cox regression hazard model			
		HR	95.0% CI		*p* value	HR	95.0% CI		*p* value
			Lower	Upper			Lower	Upper	
Age		1.029	0.939	1.128	0.544	1.039	0.990	1.090	0.12
PSA		1.000	0.999	1.000	0.566	1.000	1.000	1.000	0.89
AKP		1.001	1.000	1.002	0.027	1.000	1.00005	1.001	0.025
Visceral metastasis	No vs; yes	0.038	0.008	0.193	0.000	0.085	0.033	0.217	0.000
Bone	No vs; yes	0.434	0.043	4.399	0.480	0.206	0.028	1.537	0.123
LDH		1.000	0.999	1.001	0.585	1.001	1.0002	1.001	0.013
Albumin		0.150	0.053	0.428	0.000	0.174	0.087	0.346	0.000
Poorly differentiated Pathology	No vs; yes	8.1	0.8	79.3	0.071	0.8	0.33	2	0.66
BMI	Level I vs; level II	0.168	0.039	0.728	0.017	0.692	0.274	1.748	0.436

HR, hazard ratio; CI, confidence interval; BMI, body mass index; PSA, prostate specific antigen; LDH, Lactate dehydrogenase; AKP, Alkaline phosphatase. Values < 0.05 were considered to indicate statistical significance. Poorly differentiated pathology, Gleason score 8–10.

In addition, obesity is associated with increased levels of free IGF-1, which is found to stimulate growth of prostate cell lines in vitro and be more closely related to advanced stage PC in humans [24]. Moreover, the delayed diagnosis and more advanced stage in obese men are due to lower accuracy of digital rectal examination in obese men and lower PSA values caused by obesity-related hemodilution [25,26].

A hypothesis is that the high mortality rates among those with low BMI values could be due to systemic weight loss in response to disease.

We should not forget that the presence of other studies have shown no relationship between these two factors [27–29].

Limitations

Retrospective studies almost always are criticized as the completeness of data is often suboptimal and depends totally on medical documentation beside the small sample size in the present study. Unfortunately the data on smoking and competing risk factors that may distort the relation between excess BMI and PC mortality are not available. Despite this limitation, for our knowledge, this is the first such study in this field in King Saudi Arabia.

Conclusion & recommendation

Our data suggest that BMI is a dependent prognostic factor in patients with MPC. The cumulative survival probability was observed to improve more in patients with low BMI.

In addition, serum AKP level, serum LDL, serum albumin and visceral metastasis are independent prognostic factors.

Further prospective and large-scale multi-institutional studies are needed to evaluate the role of BMI measured before, at, or after PC diagnosis. Also, evaluation of genetic and biomarkers related to adiposity can guide the development of effective and targeted cancer prevention and therapeutic options.

Ethical consideration

Ethical approval to conduct the study was taken from the IRB review committee before the commencement of the study.

Conflict of interest

The authors certify that there is no potential or actual conflict of interest related to this research.

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