

Influence of Body Mass Index and Total Testosterone Level on Biochemical Recurrence Following Radical Prostatectomy

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Objective: A high body mass index (BMI) and a low testosterone level were recently reported to be prognostic factors for prostate-specific antigen (PSA) recurrence following radical prostatectomy (RP). The goal of this study was to clarify their relationship and influences on biochemical recurrence after RP.

Methods: We analysed 126 patients whose data, including the pre-operative BMI and pre-operative serum total testosterone level, were available. All patients underwent RP at our institution between March 1998 and April 2006 without any adjuvant therapy or pelvic lymph node metastasis. The Cox proportional hazards model was used for the multivariate analysis regarding PSA recurrence for the variables of age, operation period, BMI, clinical stage, PSA, Gleason's sum, pre-operative serum total testosterone level and margin status.

Results: There were no internal correlations among the parameters we used, even between BMI and the total testosterone level. The total testosterone level was not different between two BMI groups (BMI <26.4 and ≥ 26.4 kg/m²: the cut-off is the mean + 1 SD). BMI, PSA and Gleason's sum were found to be independent predictors for PSA recurrence through the multivariate analysis. PSA recurrence-free survival rates at 2 years were 77% for BMI <26.4 kg/m², and 31% for BMI ≥ 26.4 kg/m² ($P = 0.002$, log-rank test, 95% CI: 1.489–7.726).

Conclusions: The current study suggests that high BMI independently contributes to PSA recurrence but that the total testosterone level does not. Although the mechanism by which obesity promotes PSA recurrence in RP patients has not been established, careful observation is needed for patients with high BMI.

Keywords: body mass index – total testosterone – biochemical recurrence – PSA – radical prostatectomy – multivariate analysis

INTRODUCTION

Radical prostatectomy (RP) is the first-line treatment for organ-confined prostate cancer, and improves the survival more than watchful waiting (1). Several prognostic factors have been proposed for biochemical recurrence or survival following RP such as the pre-operative prostate-specific antigen (PSA) level and pathological features, including the Gleason sum and a positive surgical margin (2). A high body mass index (BMI) was reported to influence the

detection rate of prostate cancer in an epidemiological survey (3). Recently, there have been numerous reports that obesity also affects PSA recurrence following RP (4–6). However, the mechanism by which obesity is related to the incidence and prognosis of prostate cancer is still controversial. One of the possible mechanisms is its influence on the testosterone level (6). Late-onset hypogonadism has been reported to be related to obesity, and a low testosterone level has been suggested to relate to poor pathological features (7,8). Thus, in this study, we investigated the influences of BMI, the pre-operative testosterone level and their relationship on biochemical recurrence following RP.

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PATIENTS AND METHODS

We retrospectively investigated the clinical courses of 188 prostate cancer patients who underwent RP at our institution between March 1998 and April 2006. Pre-operative total testosterone levels were available in 140 of 188. Patients who underwent adjuvant therapy (pre-operative neoadjuvant, 4; postoperative adjuvant, 4) and those with pathologically confirmed positive lymph node metastases (6) were excluded. Finally, 126 of the 188 patients were available for this assessment. Pre-operative serum PSA concentrations were measured by ECLusys PSA II assay (Roche Diagnostics, Tokyo, Japan). BMI was calculated from the pre-operative data. PSA was obtained at 4 weeks following surgery, and after that it was assessed every 3 months. Biochemical recurrence was defined as PSA elevation above 0.2 ng/ml. Clinical staging was based on the Japanese version of the TNM classification advocated by the Japanese Urological and Pathological Associations (9). All pathological specimens were reviewed by a pathologist in 2006. The serum total testosterone level was measured by enzyme immunoassay from a blood sample taken between 8 and 11 AM. A patient was considered to be hypogonadal if he had a total testosterone level below 270 ng/dl as this was previously reported to have a relationship with poor pathological features (10).

All procedures were performed by the open retropubic RP and with the retrograde manner, which was introduced by

Walsh (11). The limited lymph node dissections of obturator fossa were performed bilaterally.

On the basis of previously reported analyses, we chose the following factors: (i) age, (ii) the period of surgery (1998–2002 versus 2003–2006), (iii) BMI, (iv) clinical stage, (v) pre-operative PSA, (vi) the Gleason sum of surgical specimen, (vii) pre-operative total testosterone level and (viii) surgical margin status. The surgery period was divided into the last 3 years and before that.

Employing StatView 5.0 (SAS Institute, Cary, NC, USA) for statistical analyses, we used the Mann–Whitney *U*-test and Student's *t*-test for statistical analysis of comparisons among groups for the patients' characteristics. The PSA recurrence-free survival was calculated using the Kaplan–Meier method. We carried out univariate analysis with the log-rank test and multivariate analysis with the Cox proportional hazards model. A *P*-value of <0.05 was considered statistically significant.

RESULTS

Table 1 shows the patients' characteristics. The patients were all Japanese. One (0.8%) was categorized as obese (BMI ≥ 30 kg/m²), 44 (34.9%) as overweight (BMI 25–30 kg/m²) and 81 (64.3%) as being of normal weight (BMI ≤ 25 kg/m²). In this study, we used BMI 26.4 kg/m² as the cutoff for 'high BMI' from the mean BMI + 1 SD

Table 1. Patients' characteristics

	BMI < 26.4, <i>n</i> = 109	BMI \geq 26.4, <i>n</i> = 17	Overall, <i>n</i> = 126
Age (years)	69 (55–77)	66 (52–73)	69 (52–77)
Surgical period: 1998–2002/2003–04/2005–06	12/51/46	1/8/8	13/59/54
BMI (kg/m ²)	23.6 (17.4–25.9)	27.5** (26.4–31.3)	24.0 (17.4–31.3)
PSA (ng/ml)	7.7	6.1 (2.9–90.8)	7.3 (1.4–90.8)
Total testosterone (ng/dl)	394 (102–1026)	338 (205–663)	385 (102–1026)
Clinical stage: 1c/2a/2b/3a	53/46/9/1	8/7/2/0	61/53/11/1
Prostate volume (cm ³)	28.5 (12.6–91.7)	29.0 (19.4–58.0)	28.5 (12.6–91.7)
Operative time (min)	205 (119–405)	235* (140–420)	210 (119–420)
Amount of bleeding (ml)	1000 (230–5300)	1400* (550–7200)	1000 (230–7200)
Nerve-sparing: none/unilateral/bilateral	75/21/13	10/6/1	87/26/14
Pathological stage (<i>n</i>): 2a/2b/3a/3b	17/42/46/4	5/5/6/1	22/47/52/5
Gleason sum	7 (6–9)	7 (6–9)	7 (6–9)
Maximum tumor diameter (mm)	13 (2–42)	10 (3–42)	13 (2–42)
Surgical margin + (%)	30 (27.5)	3 (17.6)	33 (26.2)
PSA failure + (%)	22 (19.6)	8* (41.6)	30 (23.0)
Follow-up period (months)	17 (1–84)	23 (2–50)	17 (1–84)

Most values are shown as medians (range).

P* < 0.05, *P* < 0.01 (Mann–Whitney *U*-test and Student's *t*-test).

BMI, body mass index; PSA, prostate-specific antigen.

Table 2. Univariate and multivariate analyses for PSA recurrence (log-rank and Cox proportional hazards model)

Variable	Univariate log-rank	Multivariate Cox proportional hazards model		
	<i>P</i> value	Odds ratio	95% CI	<i>P</i> value
Age (continuous)	70; 0.395	0.94	0.876–1.006	0.072
Surgical period (98–2002 versus 2003–06)	0.027	1.03	0.376–2.825	0.952
BMI (≥ 26.4 versus <26.4)	0.002	3.53	1.289–9.677	0.014
Total testosterone (≥ 270 versus <270)	0.789	2.26	0.469–10.891	0.309
PSA (continuous)	10; <0.001	1.03	1.009–1.059	0.007
T1c (no versus yes)	0.003	2.17	0.877–5.502	0.102
Gleason sum (>8 versus ≤ 8)	<0.001	5.35	1.921–14.878	0.043
Surgical margin (yes versus no)	0.011	1.67	0.718–3.898	0.233

CI, confidence interval; T1c, clinical stage T1c disease.

because the generally accepted BMI of over 30 kg/m² was not practical (only one patient) for this study. The backgrounds of the two BMI groups were different in terms of surgery-related parameters (time and blood loss) and the PSA failure rate (Table 1). No patients died during this study period.

To elucidate the prognostic factors for biochemical recurrence following RP, we evaluated them with univariate and multivariate analyses (Table 2). In the univariate analysis, every parameter except age and the total testosterone level showed statistical significance. We carried out multivariate analysis with the Cox proportional hazards model using these parameters. Gleason’s sum showed statistical difference over eight in univariate analysis, thus we took it for the cut-off for the multivariate analysis. Finally BMI, PSA, and the Gleason sum were identified as statistically significant factors (Table 2). The odds ratio was 3.53 for ‘BMI’, 1.03 for ‘PSA’ and 5.35 for Gleason sum. We could not find any internal correlation between BMI and the total testosterone level even with the other BMI cut-off point other than 26.4 kg/m². The correlation coefficients among the parameters used in this study were all below 0.1.

We estimated survival following RP with the Kaplan–Meier method (Fig. 1). The recurrence rate was significantly higher in the high BMI group (≥ 26.4 kg/m²) (*P* = 0.002, log-rank test, 95% CI: 1.489–7.726) than in the low BMI group. The biochemical recurrence-free survival rates at 1, 2 and 3 years were estimated to be 88, 77 and 64% for BMI <26.4 kg/m² and 68, 31 and 31%, respectively, for BMI ≥ 26.4 kg/m².

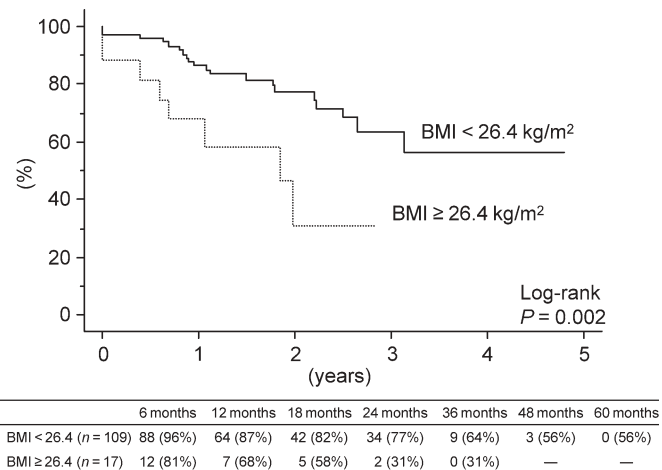


Figure 1. Prostate-specific antigen recurrence following radical prostatectomy in each group. Kaplan–Meier method. BMI, body mass index.

DISCUSSION

We set out to determine whether high BMI and total testosterone would influence PSA recurrence following RP. High BMI has been reported to influence prostate cancer detection and high-grade cancer (3,5,12,13). Recently, High BMI has also been suggested to be an independent predictor for PSA recurrence following the surgery (14–16). Very obese patients (BMI ≥ 35 kg/m²) were 1.69 times more likely to have recurrence relative to men of normal weight (BMI < 25.0 kg/m²) (17).

One of the possible mechanisms for the poor prognosis in obese patients is their poor pathological features. Freedland et al. (15) reported that obesity affected the Gleason score, positive surgical margin, capsular invasion, and lymph node metastasis. Furthermore, it has been suggested that BMI is positively related to capsular incision, because open RP is technically more difficult in obese men, which results in a greater likelihood of a less than technically ideal operation (18). Indeed, in the current study, we recognized the poor surgical quality in the high BMI group; technical difficulty could lead to longer surgical time and more blood loss than in the normal BMI group. However, we could not find any adverse pathological features, including the surgical margin, even in these technically less-ideal operations. On the other hand, there was another report that long-term oncologic outcomes, including cancer-specific survival, remained the same regardless of BMI, despite these poor pathological features (4). Thus far, the involvement of poor pathological features in biochemical recurrence among obese patients is still controversial, so it will need further investigation (19).

As other possible mechanisms, steroid hormones, including testosterone, or obesity-related cytokines such as leptin, adiponectin, insulin and IGF-1 were proposed to be candidates (20–23). Recently, late-onset hypogonadism has been reported to induce obesity (8). Patients with low total testosterone also more frequently present with poor pathological features, including capsular invasion and positive surgical

margins in RRP specimens (7,10,24). Moreover, there is a report that obesity is associated with lower serum testosterone levels and a higher risk of biochemical recurrence and prostate cancer-specific death after radiation therapy (25). In our study, we could not find any relationship between the total testosterone level and biochemical recurrence after RP. Nor did we find any relationship between the total testosterone level and BMI. However, this might have been influenced by the method of testosterone measurement. Bioavailable testosterone, which is biologically active testosterone, is affected by the sex hormone-binding globulin (SHBG) level, which is influenced by aging and obesity itself (26). Thus, we need to confirm the relationship between the bioavailable testosterone level and obesity in a large-scale study to elucidate this in the near future. However, high BMI itself might have strongly influenced biochemical recurrence independently, because we could not find any poor pathological feature or low testosterone among obese patients in the current study. The mechanism is still unclear; however, adiposity-related cytokines such as adiponectin and leptin might influence cancer aggressiveness following surgery as recently reported (20,23). If so, as a treatment strategy, a diet reducing the visceral fat after surgery might be effective to inhibit biochemical recurrence, although we need the further investigations regarding the fat distribution (subcutaneous or visceral), the detailed adipose tissue characteristics, or the obesity related cytokine level itself in future.

In our study population, only one patient (0.8%) was categorized as 'obese' (BMI ≥ 30 kg/m²), which is a much lower rate than in reports from other countries. This could be explained by a racial difference, as the rate of Japanese with a BMI ≥ 30 kg/m² was reported to 3%, whereas it was 30% in Americans (27). Furthermore, BMI may account, in part, for the racial variability in prostate cancer risk, because black men have higher recurrence rates and a greater BMI than white men (28). Racial differences in the mortality rates of prostate cancer are multifactorial and the exact reasons are still controversial (29,30). Whether the racial difference in obesity is related to the racial difference in prostate cancer-related mortality needs further investigation.

Our study is the first report investigating the relationships among biochemical recurrence, BMI, and the testosterone level after RP. However, there are some limitations of this study we need to address, including the limited postoperative follow-up period, and that the surgeon was not a single person because of the institutional character as a surgery training center. We should clarify the involvement of bioavailable testosterone and other factors in biochemical recurrence through an extended time course for both the biochemical recurrence and cancer-specific survival in the future.

CONCLUSIONS

Although the exact mechanism by which obesity contributes to biochemical recurrence of prostate cancer following

radical RP has not been established yet, obesity is an independent risk factor for the recurrence. We should closely monitor patients with high BMI (≥ 26.4 kg/m² in this study) following surgery hereafter.

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Conflict of interest statement

None declared.

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