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Change of preoperative symptoms of the late-onset hypogonadism syndrome after robot-assisted radical prostatectomy

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Abstract

Background: As prostate cancer (PCa) is a common cancer among older men, patients with PCa often show aging male symptoms (AMSs). This study aimed to investigate the preoperative AMSs of the late-onset hypogonadism (LOH) syndrome and the effects on them after robot-assisted radical prostatectomy (RARP).

Materials and methods: One hundred eighty-eight patients who underwent RARP without androgen deprivation therapy were measured for serum free and serum total testosterone, and were preoperatively assessed for symptoms of the LOH syndrome using a questionnaire containing an AMS score. Patients with a preoperative AMS score higher than 37 and a serum free testosterone level lower than 8.5 pg/mL were classified as Group A, with the remaining classified as Group B. AMS scores were measured at 1, 3, 6, 9, and 12 months after surgery.

Results: Of the 188 patients, 49 and 139 patients were classified as Groups A and B, respectively. Preoperative AMS scores were 44.5±8.2 in Group A and 28.6±5.3 in Group B ($p<0.0001$). AMS scores in Group A significantly improved 1 month after RARP (30.6±8.4, $p<0.0001$) compared with their preoperative scores and remained at the same level from 3 to 12 months postoperatively, whereas those in Group B became significantly worse (32.0±7.8, $p<0.0001$) than their preoperative ones. There were no differences between AMS scores in Groups A and B at every postoperative period ($p=0.3259$, 0.2730, 0.2429, 0.4629, 0.1771 at 1, 3, 6, 9, and 12 months after surgery, respectively).

Conclusions: Our results indicate that AMSs in PCa patients with the LOH syndrome can expect the same level of improvement as patients without it.

Keywords: Aging male symptoms; Late-onset hypogonadism; Prostate cancer; Robot-assisted radical prostatectomy; Testosterone

1. Introduction

Prostate cancer (PCa) is one of the most common malignant diseases among men. Although the widespread use of prostate-specific antigen screening has led to an increase of the prevalence of PCa with localized stage, there are various therapeutic options including radical prostatectomy (RP), radiation therapies, and active surveillance for localized PCa. Because patients with localized PCa have a longer life-expectancy, both patients and physicians are required to make the most appropriate treatment decisions. It is essential to consider the health-related quality of life (HRQOL) and adverse effects for each treatment option.

Many previous studies have demonstrated the effects of primary treatment such as RP on the QOL in patients.[1–3] Although open RP (ORP) and laparoscopic RP have been established as standard surgical procedures for localized PCa, postoperative urinary incontinence and sexual dysfunction are serious concerns. Robot-assisted RP (RARP) has rapidly spread too many countries including Japan. Systemic reviews have demonstrated the benefits of RARP in postoperative recovery of urinary continence and sexual function compared with ORP and laparoscopic RP.[4,5]

The late-onset hypogonadism (LOH) syndrome is a biochemical and clinical syndrome characterized by decreased serum testosterone levels and aging male symptoms (AMSs) in aging men.[6,7] The prevalence of male patients with the LOH syndrome increases with age.[8] Since PCa is a common cancer among older men, patients with PCa often exhibit AMSs. However, there are no reports clarifying the effect of RARP on AMS. This study aimed to investigate the preoperative AMSs of the LOH syndrome and the effects on them after RARP.

2. Patients and methods

One hundred eighty-eight patients who underwent RARP without androgen deprivation therapy were retrospectively investigated by reviewing clinicopathological data. Ethical approval was given by the Ethical Committee of Hiroshima

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Table 1
Characteristics of patients.

	Group A ($n=49$)	Group B ($n=139$)	p	Total ($n=188$)
Median age, y	66 (52–77)	67 (48–77)		67 (48–77)
Median preoperative PSA, ng/mL	7.54 (2.6–22.5)	6.7 (0.62–57.1)	0.6449	6.79 (0.62–57.1)
Clinical stage, *n* (%)				
T1–T2a	45 (91.8)	111 (79.9)	0.0550	156 (83.0)
T2b–T2c	4 (8.2)	26 (18.7)		30 (16.0)
T3	0 (0)	2 (1.4)		2 (1.1)
Biopsy GS, *n* (%)				
≤6	8 (16.3)	36 (25.9)	0.1736	44 (23.4)
7	32 (65.3)	77 (55.4)		109 (58.0)
8–10	9 (18.4)	26 (18.7)	0.9584	35 (18.6)
D'Amico risk, *n* (%)				
Low	6 (12.2)	29 (20.9)	0.1826	35 (18.6)
Intermediate	30 (61.2)	72 (51.8)		102 (54.3)
High/very high	13 (26.5)	38 (27.3)	0.9130	51 (27.1)
Nerve sparing, *n* (%)				
No	25 (51.0)	92 (66.2)	0.0597	117 (62.2)
Unilateral	12 (24.5)	29 (20.9)		41 (21.8)
Bilateral	12 (24.5)	18 (13.0)	0.0579	30 (16.0)
Pathological T stage, *n* (%)				
T2	43 (87.8)	112 (80.6)	0.2560	155 (82.4)
≥T3a	6 (12.2)	27 (19.4)		33 (17.6)
Pathology GS, *n* (%)				
≤6	5 (10.2)	6 (4.3)	0.1311	11 (5.9)
7	37 (75.5)	111 (79.9)		148 (78.7)
8–10	7 (14.3)	22 (15.8)	0.7973	29 (15.4)

GS = Gleason score; PSA = prostate-specific antigen.

University (Allowance notification number: E-107-2), and all the patients agreed to participate and signed informed consent forms with guarantees of confidentiality.

AMSs in patients were evaluated by a score (AMS score) that was previously well validated.[9,10] Patients with preoperative AMS scores higher than 37 and serum-free testosterone levels lower than 8.5 pg/mL were classified as Group A, whereas those whose preoperative AMS scores were 37 or lower, or whose serum-free testosterone level were 8.5 pg/mL or higher, were classified as Group B, in accordance with the criteria previously described.[11,12] AMS scores were measured at 1, 3, 6, 9, and 12 months after surgery. Patients were measured for serum free and serum total testosterone and were assessed preoperatively.

All statistical analyses were conducted using Statview 5.0 (Abacus Concepts, Inc., Berkeley, CA). Differences in the distribution of categorical variables and continuous ones among groups were analyzed using the chi-square test and the Mann–Whitney *U* test, respectively. The Wilcoxon's test was conducted between the scores and serum testosterone levels of each observation period. The significance criteria of these analyses were set at a p value of <0.05.

3. Results

Our analysis was based on the 188 patients who provided longitudinal follow-up information on their AMSs. Of the 188 patients, 49 and 139 patients were classified as Groups A and B, respectively. There were no significant differences in patient characteristics between the groups (Table 1). The numbers of patients who remained evaluable at the measurement points 1, 3, 6, 9, and 12 months after RARP were 158 (84.0%), 146 (77.7%), 145 (77.1%), 148 (78.7%), and 131 (69.7%) in all patients, 45 (91.8%), 40 (81.6%), 40 (81.6%), 40 (81.6%), and 37 (75.5%) in Group A, and 113 (81.3%), 106 (76.3%), 105 (75.5%), 108 (77.7%), and 94 (67.6%) in Group B, respectively. Preoperative AMS scores in Group A were significantly worse than those in Group B (Table 2). There were no significant differences in preoperative serum levels between these 2 groups in either serum free or serum total testosterone ($p=0.7601$ and 0.4229, respectively, Fig. 1) whereas preoperative serum free testosterone levels in all patients in Group A were lower than 8.5 pg/mL. Serum-free testosterone levels in Group B significantly decreased postoperatively, whereas there was no significant change between pre- and postoperative serum levels of total and free testosterone in Group A. AMS scores in Group A significantly improved 1 month after RARP compared with their preoperative ones and remained at the same level from 3 to 12 months postoperatively, whereas those in Group B became significantly worse than their preoperative ones. There was no significant differences between AMS scores in Groups A and B in every postoperative period (Fig. 2) (Table 2). In all subscales including somatic, sexual, and psychological ones, preoperative scores were significantly worse in Group A than those in Group B ($p<0.0001$) (Fig. 3) (Table 2). In every subscale, scores significantly improved in Group A and those in Group B became worse 1 month after surgery and remained at the same level for 1 year. Also, every component of the longitudinal data showed the same change patterns in the total AMS score (Fig. 3) (Table 2).

4. Discussion

The study investigated AMSs in PCa patients who underwent RARP. Patients with the LOH syndrome might be expected to improve at the same level as those free from it postoperatively. To

Table 2

Preoperative and postoperative AMS scores.

	Group A	Group B	*p*	Total
Total score (mean ± SD)				
Preoperative	44.5 ± 8.2	28.6 ± 5.3	<0.0001	32.7 ± 9.3
1 month after surgery	30.6 ± 8.4	32.0 ± 7.8	0.3259	31.6 ± 8.0
3 months after surgery	31.6 ± 8.3	33.0 ± 8.6	0.2730	32.6 ± 8.5
6 months after surgery	34.7 ± 10.9	32.0 ± 9.4	0.2429	32.7 ± 9.9
9 months after surgery	33.1 ± 7.9	32.4 ± 9.4	0.4629	32.6 ± 9.0
12 months after surgery	30.4 ± 7.9	32.7 ± 9.2	0.1731	32.0 ± 8.8
Somatic subscale (mean ± SD)				
Preoperative	17.0 ± 3.9	10.6 ± 2.7	<0.0001	12.2 ± 4.1
1 month after surgery	10.7 ± 3.7	12.1 ± 3.3	0.0166	11.7 ± 3.4
3 months after surgery	11.6 ± 3.8	11.8 ± 3.6	0.5580	11.8 ± 3.6
6 months after surgery	13.2 ± 5.2	11.6 ± 4.0	0.1493	12.0 ± 4.4
9 months after surgery	12.1 ± 3.1	12.5 ± 3.8	0.6410	12.4 ± 3.6
12 months after surgery	12.1 ± 4.0	12.3 ± 4.1	0.7786	12.2 ± 4.0
Psychological subscale (mean ± SD)				
Preoperative	10.1 ± 3.9	5.9 ± 1.7	<0.0001	7.0 ± 3.1
1 month after surgery	6.7 ± 2.2	7.0 ± 2.5	0.4618	6.9 ± 2.5
3 months after surgery	6.8 ± 2.6	7.1 ± 2.7	0.4691	7.0 ± 2.7
6 months after surgery	7.8 ± 3.2	7.1 ± 3.0	0.2272	7.3 ± 3.0
9 months after surgery	7.1 ± 2.6	7.4 ± 3.1	0.7282	7.3 ± 3.0
12 months after surgery	7.0 ± 2.7	7.3 ± 2.9	0.6454	7.2 ± 2.9
Sexual subscale (mean ± SD)				
Preoperative	17.4 ± 2.9	12.1 ± 3.8	<0.0001	13.5 ± 4.3
1 month after surgery	13.2 ± 4.4	13.0 ± 4.2	0.6844	13.1 ± 4.2
3 months after surgery	13.2 ± 3.9	14.0 ± 4.1	0.1925	13.8 ± 4.1
6 months after surgery	13.7 ± 4.7	13.3 ± 4.5	0.6518	13.4 ± 4.5
9 months after surgery	14.0 ± 4.4	12.5 ± 4.6	0.0753	12.9 ± 4.6
12 months after surgery	11.4 ± 4.2	13.1 ± 4.3	0.0177	12.6 ± 4.3

AMS = aging male symptom; SD = standard deviation.

the best of our knowledge, this is the first report to demonstrate longitudinal data of AMSs after RARP.

Although there are various active therapeutic options for localized PCa, including RP, radiation therapies, and androgen-deprived therapy, how to minimize their negative effects on urinary, erectile, and bowel- and hormone-related functions has been an ongoing concern from screening to treatment of localized PCa.[2,3] Because of such side effects or complications of treatment options, PCa survivors have had a two-fold to five-fold greater prevalence of urinary incontinence compared with people without PCa.[13]

Before RARP became widespread, a number of cross-sectional studies showed that there was no difference of the HRQOL among treatments.[14–16] The introduction of RARP has enabled patients with PCa who underwent surgical treatment to recover urinary continence and sexual function to some degree.[4,5] Furthermore, RARP has helped even expert surgeons of ORP to achieve better functional outcomes.[17] Through these many reports on the benefits of perioperative outcomes, RARP has been recognized as the standard surgical procedure for localized PCa in many countries, including Japan.

The prevalence of male patients with the LOH syndrome, which consists of AMSs and decreased testosterone, increases with age, and it leads to systemic morbidities in various organs. A previous longitudinal study demonstrated that the rate of patients with the biochemical LOH syndrome were 34% for men aged 60–69, 68% for those aged 70–79, and 91% for those aged 80 and over.[8] In addition, many studies have reported a correlation between the risk of development or progression of PCa and the serum testosterone level.[18–20] Thus, AMSs and serum testosterone levels need to be investigated in patients with PCa. However, to the best of our knowledge, there are no reports on AMSs in PCa patients after RP including RARP despite it being the most representative option of surgical procedure for localized PCa. Considering this, clarifying the longitudinal change of AMS after RARP is very important. In this study, we investigated the preoperative data, including AMSs and serum testosterone levels, and postoperative longitudinal AMS scores of patients who underwent RARP. As a result, in all subscales, the preoperative AMS scores in Group A were significantly worse than those in Group B, but the postoperative AMS scores in Group A significantly improved at the same rate as those in Group B after RARP, and remained the same for a year. Previous studies demonstrated that many of the symptom scores and components of the HRQOL, including sexual and urinary ones, became transiently significantly worse at an early period after RARP.[1–5] The pattern of the longitudinal change of AMS scores and their subscales in the present study seems to be unique compared with previous data. The reason for this discrepancy is unclear, but we have speculated as to the reason. We assessed preoperative AMS scores just before surgery, in other words, after patients were diagnosed with PCa and when they decided to receive RARP. Therefore, it is possible that the onset of the LOH syndrome in many of patients in Group A was at the time of their diagnosis, and they recovered after RARP was successfully performed. For such patients, knowing that their cancers had been removed through RARP may provide them some relief even when there are postoperative comorbidities.

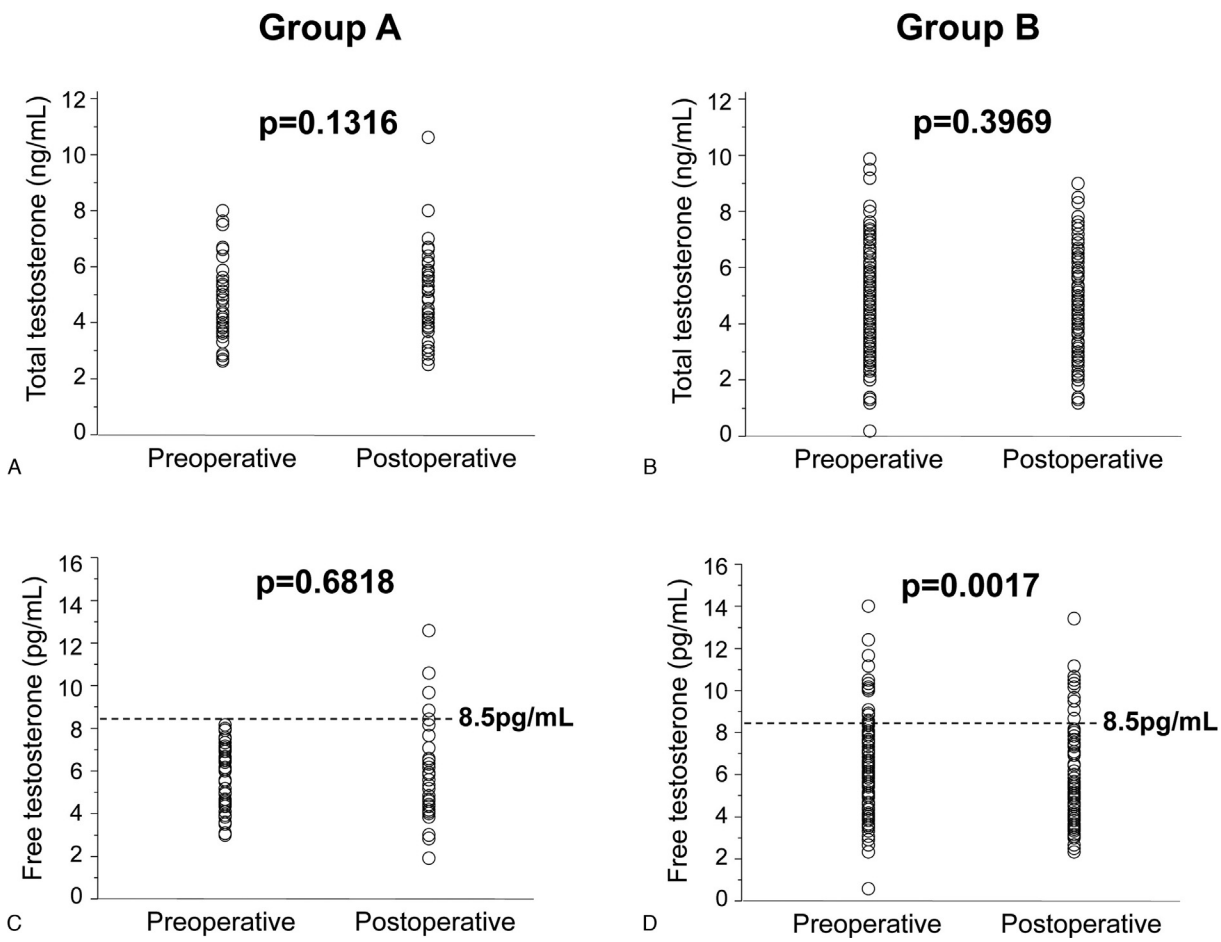

Figure 1. Comparison between preoperative and postoperative serum levels of total testosterone in (A) Group A (4.5 ± 1.4 ng/mL and 4.8 ± 1.5 ng/mL) and (B) Group B (4.5 ± 1.8 ng/mL and 4.4 ± 1.6 ng/mL), and free testosterone in (C) Group A (5.8 ± 1.5 pg/mL and 5.7 ± 2.2 pg/mL), and (D) Group B (5.7 ± 1.4 pg/mL and 6.2 ± 2.2 pg/mL), respectively.

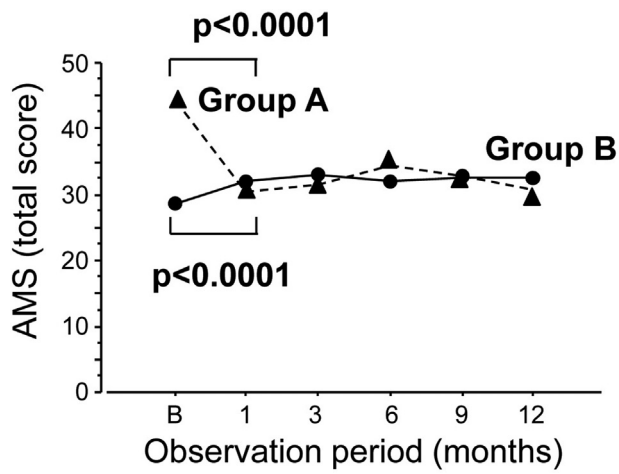

Figure 2. Longitudinal change of mean AMS score. AMS = aging male symptom; B = baseline.

The limitations of this study were its small-size and short observation period, and postoperative longitudinal changes in testosterone levels were not thoroughly discussed. Decreased testosterone levels were reported as an important component of the LOH syndrome and their association with the malignant potential or progression of PCa.[18–20] In addition, a previous study demonstrated that postoperative testosterone levels had an impact on biochemical recurrence and the replacement of testosterone affected a reduction of recurrence.[21] We found a decrease of the serum-free testosterone level in Group B and no significant difference of it in Group A. This seems to be consistent with the difference in the patterns of postoperative change between Groups A and B (Figs. 2 and 3). However, we only showed the data at 3 months after surgery, only one point within the postoperative period. There is still no longitudinal study assessing changes of serum testosterone levels after RP. Therefore, further longitudinal studies with a larger volume and a longer follow-up period are required to support our findings and to discuss the association of RARP with testosterone levels during pre- and postoperative periods.

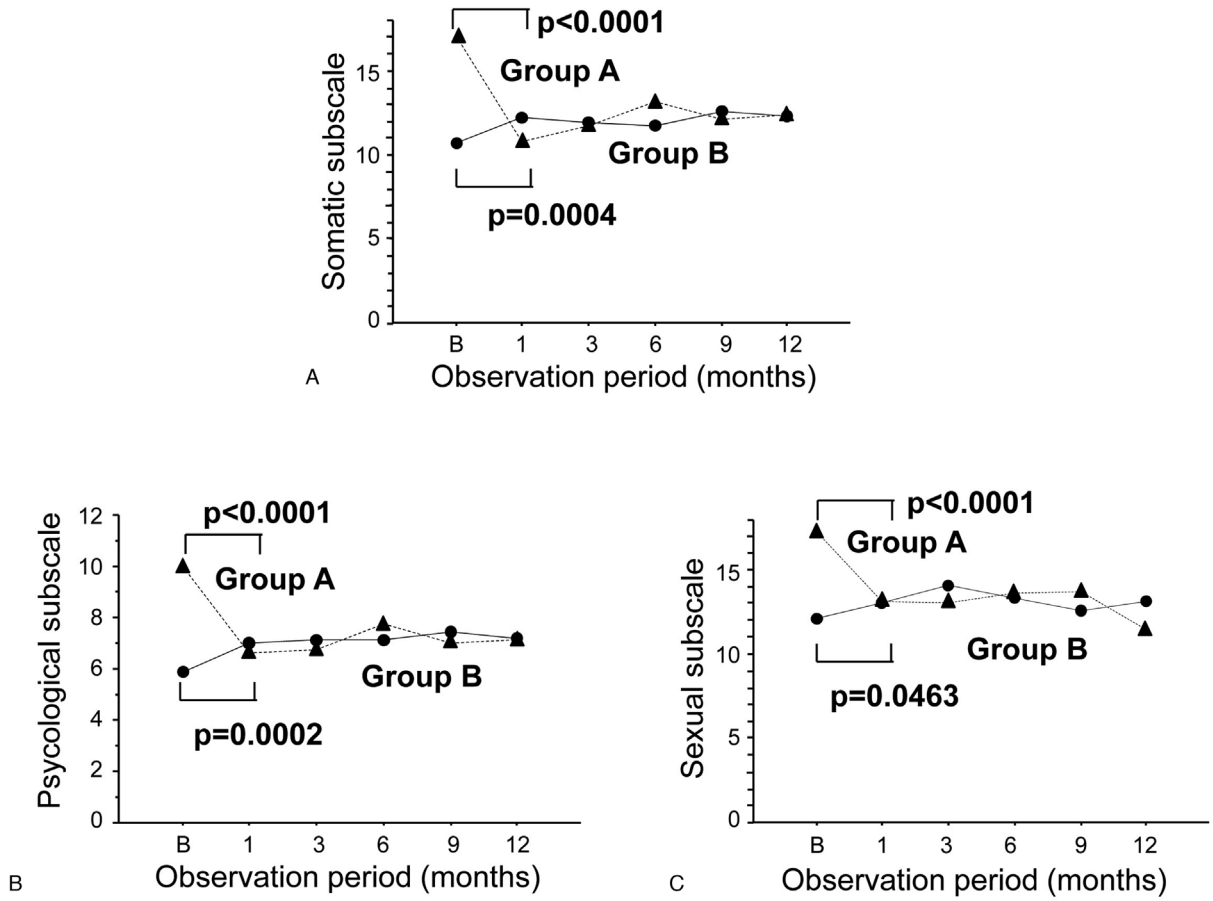

Figure 3. Longitudinal change of mean (A) somatic, (B) psychological, and (C) sexual subscales in AMS score. AMS = aging male symptom; B = baseline.

In conclusion, we demonstrated that PCa patients can recover from the symptoms of the LOH syndrome after RARP. These findings can help urologic surgeons to determine an appropriate therapeutic option for patients with localized PCa.

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None.

Statement of ethics

Ethical approval was given by the Ethical Committee of Hiroshima University.(Allowance notification number:E-107-2).

Conflict of interest statement

No conflict of interest has been declared by the author.

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None.

Author contributions

Jun Teishima: Design of the study, Data analysis, Drafting the manuscript.
Shogo Inoue: Data analysis.
Tetsutaro Hayashi: Data acquisition.
Akio Matsubara: Supervision.

References

[1] Mohamad Al-Ali B, Ponholzer A, Augustin H, Madersbacher S, Pummer K. The long-term effect of radical prostatectomy on erectile function, urinary continence, and lower urinary tract symptoms: a comparison to age-matched healthy controls. *Biomed Res Int* 2017;2017:9615080. doi: 10.1155/2017/9615080.
[2] Schröder FH, Hugosson J, Roobol MJ, et al. Prostate-cancer mortality at 11 years of follow-up. *New Engl J Med* 2012;366(11):981–990.
[3] Hamdy FC, Donovan JL, Lane JA, et al. 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *New Engl J Med* 2016;375(15):1415–1424.
[4] Ficarra V, Novara G, Rosen RC, et al. Systematic review and meta-analysis of studies reporting urinary continence recovery after robot-assisted radical prostatectomy. *Eur Urol* 2012;62(3):405–417.
[5] Ficarra V, Novara G, Ahlering TE, et al. Systematic review and meta-analysis of studies reporting potency rates after robot-assisted radical prostatectomy. *Eur Urol* 2012;62(3):418–430.
[6] Miranda EP, Torres LO. Late-onset hypogonadism: prostate safety. *Andrology* 2020;8(6):1606–1613.
[7] Huhtaniemi I, Forti G. Male late-onset hypogonadism: pathogenesis, diagnosis and treatment. *Nat Rev Urol* 2011;8(6):335–344.
[8] Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. *J Clin Endocrinol Metab* 2001;86(2):724–731.
[9] Heinemann LA, Zimmermann T, Vermeulen A, Thiel C, Hummel W. A new 'aging males' symptoms' rating scale. *Aging Male* 1999;2(2):105–114.
[10] Heinemann LA, Saad F, Zimmermann T, et al. The aging males' symptom (AMS) scale: update and compilation of international versions. *Health Qual Life Outcomes* 2003;1:15.
[11] Iwamoto T, Yanase T, Koh E, et al. Reference ranges of total serum and free testosterone in Japanese male adults. *Nihon Hinyokika Gakkai Zasshi* 2004;95(6):751–760.

[12] Liu Z, Liu J, Shi X, et al. Comparing calculated free testosterone with total testosterone for screening and diagnosing late-onset hypogonadism in aged males: a cross-sectional study. *J Clin Lab Anal* 2017;31(5): e22073.
[13] Kopp RP, Marshall LM, Wang PY, Bauer DC, Barrett-Connor E, Parsons JK. The burden of urinary incontinence and urinary bother among elderly prostate cancer survivors. Osteoporotic fractures in Men MrOS Research Group. *Eur Urol* 2013;64(4):672–679.
[14] Litwin MS, Hays RD, Fink A, et al. Quality-of-life outcomes in men treated for localized prostate cancer. *JAMA* 1995;273(2):129–135.
[15] Shrader-Bogen CL, Kjellberg JL, McPherson CP, Murray CL. Quality of life and treatment outcomes: prostate carcinoma patients' perspectives after prostatectomy or radiation therapy. *Cancer* 1997;79(10):1977–1986.
[16] McCammon KA, Kolm P, Main B, Schellhammer PF. Comparative quality-of-life analysis after radical prostatectomy or external beam radiation for localized prostate cancer. *Urology* 1999;54(3):509–516.
[17] Thompson JE, Egger S, Böhm M, et al. Superior biochemical recurrence and long-term quality-of-life outcomes are achievable with robotic radical prostatectomy after a long learning curve–updated analysis of a prospective single-surgeon cohort of 2206 consecutive cases. *Eur Urol* 2018;73(5):664–671.
[18] Hoffman MA, DeWolf WC, Morgentaler A. Is low serum free testosterone a marker for high grade prostate cancer? *J Urol* 2000;163(3): 824–827.
[19] Schatzl G, Madersbacher S, Thurridl T, et al. High-grade prostate cancer is associated with low serum testosterone levels. *Prostate* 2001;47(1):52–58.
[20] Morgentaler A, Rhoden EL. Prevalence of prostate cancer among hypogonadal men with prostate-specific antigen levels of 4.0 ng/mL or less. *Urology* 2006;68(6):1263–1267.
[21] Ahlering TE, Huynh LM, Towe M, et al. Testosterone replacement therapy reduces biochemical recurrence post-radical prostatectomy. *BJU Int* 2020;126(1):91–96.

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